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FOREWORD

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Introduction

This is the annual report for Year 03 of the project titled 'The Relationship of Exercise to Fatigue and Quality of Life in Women with Breast Cancer'. The purpose of this Year 03 report is to describe the scope of work accomplished in the past 12 months and over the 36 months of the project. The primary purpose of this study is to test the direct and indirect relationships of exercise to fatigue and quality of life in newly diagnosed women with breast cancer who were receiving chemotherapy. The following information will review the work accomplished to date, results, conclusions and future work plans.

Body

Review of Statement of Work

The Statement of Work for months 1-12 (Task 1) of the project was accomplished on schedule in year 01 of the study. The Tasks proposed for months 13-24, completion of coursework, and continued data collection were also completed in the proposed timeframe. Task 3 (months 25-36) of the project were completed according to the Statement of Work. These tasks included: completion of data entry, data analysis and manuscript preparation. Presentations, abstracts, manuscripts and awards that have resulted from this award are listed in the appendix.

Seventy-eight women with breast cancer were recruited into the study before they began chemotherapy, when they were drug naive. Although there were no adverse effects from the study intervention, eight women dropped-out of the study or were lost to follow-up. All subjects received instruction on the 8-week home-based low intensity exercise program and use of the Caltrac accelerometer and exercise logs. At baseline all subjects completed a 12-minute walk, and measures of fatigue (Profile of Mood States fatigue and vigor subscales, and visual analog scale of fatigue), and quality of life (Positive Affect Negative Affect Scale, and Quality of Life Index for patients with cancer). All of these measures were re-administered during weekly follow-up calls, except the 12-minute walk and Quality of Life Index. The 12-minute walk and Quality of Life Index were completed again at posttest. The weekly calls also served as a reminder for subjects to return their exercise and fatigue logs, and a time to answer questions about exercise. At posttest the measures were all re-administered.

Tasks for the final year of the project were completed as originally proposed. The only modification to the work plan was the decision to accept a position at University Washington. This change was effective July 1, 1998 and involved the process of grant transfer. Human Subjects approval was obtained. The move had no effect on the project

since data collection was complete in June, 1998. Data entry was ongoing throughout the study period, and was completed in the 6th month of this funding year. The work described above represents completion of the goals in Task 1, 2 and 3 of the Statement of Work.

Findings

Two new analyses have been conducted to examine the mediating effect of fatigue and pattern of weight change in women with breast cancer. The next two sections describe the findings of each of these analyses.

Analysis 1: Weight gain is a common side effect for women receiving adjuvant chemotherapy that is distressing and may have negative long-term implications for survival. The purpose of this analysis was to examine the effects of an exercise program on women with breast cancer receiving adjuvant chemotherapy. Seventy-eight newly diagnosed women with breast cancer who were beginning adjuvant chemotherapy were enrolled in a home-based exercise study during the first 3 cycles of chemotherapy. Weight change, body mass index, anorexia, nausea, caloric expenditure during exercise and functional ability were recorded. Women who adhered to the exercise program maintained their body weight, while nonexercisers steadily gained weight (Table 1). There were no differences in incidence or intensity of nausea or anorexia between the exercisers and nonexercisers. Women who exercised over the 4 cycles of chemotherapy improved their functional ability (23%) compared to the nonexercisers who showed significant declines in functional ability (-15%). Exercise may be an effective intervention to minimize weight gain in women with breast cancer receiving adjuvant chemotherapy. Preventing weight gain in these patients may be important in preventing recurrent disease and other comorbidities associated with excess weight.

Table 1. Differences in weight between exercisers and nonexercisers.

	Sum Squares	df	F	p
2 nd chemo				
between	1824	1	2.9	.10
within	14700	24		
total	16524	25		
3 rd chemo				
between	3445	1	6.2	.02
within	10062	18		
total	13508	19		
4 th chemo				
between	5828	1	6.6	.02
within	30082	34		
total	35909	35		

Analysis 2: Exercise and daily fatigue pattern

The purpose of this analysis was to describe the pattern of fatigue in women with breast cancer women who did and did not exercise while receiving adjuvant chemotherapy. Women received instruction to follow an 8-week home-based exercise program and maintain daily exercise and fatigue diaries. Functional ability (12-minute walk) was measured at pretest and posttest. Several distinct patterns of fatigue emerged. The most common pattern of fatigue after chemotherapy demonstrated a sharp rise in fatigue. However, several women demonstrated a chaotic pattern with erratic and wide swings in their fatigue. Women who adopted exercise experienced fewer days of fatigue above their baseline and more days of fatigue below baseline (Table 2). Women who did

not exercise experienced more days of high fatigue and fewer days of low fatigue.

Exercise appears to reduce fatigue and help women recognize their pattern of fatigue.

Table 2. Pattern of peak average and worst fatigue with each chemotherapy cycle *.

	N	Exercisers (n)	Non-exercisers (n)	χ^2	p
Average fatigue (n=17)					
↓ peak fatigue with each chemotherapy cycle	11	10	1	2.88	.09
↑ peak fatigue with each chemotherapy cycle	6	2	4		
Worst fatigue (n=15)					
↓ peak fatigue with each chemotherapy cycle	13	11	2	8.07	.005
↑ peak fatigue with each chemotherapy cycle	2	0	2		

*Reflects only subjects who fit into this pattern of fatigue.

Conclusions

The findings of both analyses support exercise as an intervention for fatigue in women with breast cancer who are receiving chemotherapy. Conclusions from analysis 1 suggest that the low intensity, home-based exercise program was feasible for women with breast cancer receiving chemotherapy, and resulted in improved functional ability and quality of life in subjects who exercised. The combination of maintaining weight and improving functional ability during chemotherapy may be an unusual outcome to expect for women with breast cancer receiving adjuvant chemotherapy. However, a clinical paradigm change may be evolving as preliminary evidence mounts in support of exercise as an intervention to minimize weight gain, reduce fatigue, improve functional ability, mood and diseases of disuse that often accompany cancer treatment (Dimeo, 1997, 1998; Mock, 1994, 1997; Schwartz, 1998; Schwartz, 1999; Schwartz, Mori, Gao, Nail, King, Madsen, 1999). Exercise has also been suggested to have a protective effect against the development of breast cancer in young women (Bernstein et al 1994), and older women (Coogan et al, 1997; McTiernan, et al, 1996) and is clearly linked to reducing risks for other co-morbid conditions that decrease quality of life, and cause significant morbidity, mortality and expense (Blair et al, 1995; Paffenbarger et al, 1993; Raven, Barrett-Conner & Edelstein, 1991).

Findings from analysis 2, suggest that exercise may have a positive effect on fatigue, may help women with breast cancer re-organize their interpretation of fatigue, and learn to manage their symptoms more quickly. Understanding the response-shift in fatigue may lead to future research examining how cognitive structures that are involved in reorganize a patient's understanding of fatigue are formed and how this reorganization affects responses to measures of fatigue and other symptoms (Breetvelt & VanDam, 1991). To keep women with breast cancer functioning and participating in activities they

value it is critical that we develop interventions to promote functional ability and minimize side effects.

In conclusion, the project was completed as planned in the Statement of Work. No adverse events were observed and results are promising. Future research will examine the effects of catabolic steroids on fatigue, weakness, body composition and quality of life.

References

- Bernstein, L., Henderson, B.E., Hanish, R., Sullivan-Halley, J., & Ross, R.K.: Physical exercise and reduced risk of breast cancer in young women. *J. Natl Cancer Inst*, 86, 1403-8, 1994.
- Blair, S.N., Kohl, H.W., Barlow, C.E., Paffenbarger, R.S., Gibbons, L.W., Macera, C.A.: Changes in physical fitness and all-cause mortality. *JAMA* 273:1093-1098, 1995.
- Breetvelt, I.S., & Van Dam, F.S.A.M. Underreporting by cancer patients: the case of response shift. *Soc Sci Med*, 1991;32 (9):981-987.
- Coogan, P.F., Newcomb, P.A., Clapp, R.W., Trentham-Deitz, A., Baron, J.A., & Longnecker, M.P.: Physical activity in usual occupation and risk of breast cancer (United States). *Cancer Causes Control* 8: 626-31, 1997.
- Dimeo, F., Rumberger, B.G., & Keul, J.: Aerobic exercise as therapy for cancer fatigue. *MSSE* 30: 475-478, 1998.
- Dimeo FC, Tilmann MHM, Bertz H, Kanz L, Mertelsmann R, Keul J.: Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous stem cell transplantation. *Cancer*, 79: 1717-22, 1997.
- Dimeo FC, Fetscher S, Lange W, Mertelsmann R, Keul J.: Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood*, 90: 3390-94, 1997.
- McTiernan, A., Stanford, J.L., Weiss, N.S., Daling, J.R., & Voigt, L.F.: Occurrence of breast cancer in relation to recreational exercise in women age 50-64 years. *Epidemiology*, 7: 598-604, 1996.
- Mock V, Burke MB, Sheehan P, Creaton EM, Winningham ML, McKenney-Tedder S, Schwager, L.P., & Liebman, M.: A nursing rehabilitation program for women

with breast cancer receiving adjuvant chemotherapy. *Onc Nurs Forum*, 21, 899-907, 1994.

Mock V, Dow KH, Meares CJ, Grimm PM, Dienemann JA, Haisfield-Wolfe ME, Quitasol, W., Mitchell, S., Chakravarthy, A., & Gage, I.: An exercise intervention for management of fatigue and emotional distress during radiotherapy treatment for breast cancer. *Oncology Nursing Forum*, 24: 991-1000, 1997.

Paffenbarger, R.S. Hyde, R.T., & Wing, A.L.: Physical activity and incidence of cancer in diverse population: a preliminary report. *Amer J Clin Nut* 45:312-317, 1987.

Raven,

Schwartz A.L.: Patterns of exercise and fatigue in physically active cancer survivors. *Oncol Nurs Forum* 25: 485-491, 1998.

Schwartz, A.L.: Fatigue mediated the effects of exercise on quality of life. *Quality of Life Research* accepted, 1999.

Schwartz, A.L., Mori, M., Gao, R., Nail, L.M., King, M.E., & Madsen, S.: Exercise Dose and Fatigue: Day to Day Variation in Women with Breast Cancer. *Nursing Research* in review, 1999.

Appendix

Presentations resulting from this support:

- 5/99 Effect of exercise on weight gain in women with breast cancer receiving adjuvant chemotherapy. American Society of Clinical Oncology, Atlanta, GA.
- 5/99 Exercise dose and daily pattern of fatigue. Oncology Nursing Society, Atlanta, GA.
- 4/99 Fatigue: Issues in management, measurement and research. Southwest Oncology Group (SWOG) Nursing Plenary Session, Phoenix, AZ
- 4/99 Fatigue: Managing a difficult treatment side effect. Eugene, OR
- 4/99 Differences in the pattern of cancer-related fatigue and vigor. Western Institute of Nursing, San Diego, CA.
- 4/99 Managing fatigue in the clinical setting. Foundations in chemotherapy practice, Shoreline, WA
- 4/99 Management Issues: fatigue. Providence Hospital, Portland, OR
- 3/99 Keys to developing and exercise program for cancer patients. Enhancing Care: 3rd Annual Conference on Fatigue and Quality of Life, Philadelphia, PA
- 3/99 Exercise in the management of cancer-treatment related fatigue. Enhancing Care: 3rd Annual Conference on Fatigue and Quality of Life, Philadelphia, PA
- 2/99 Exercise dose and daily pattern of fatigue. Paper presented at the 5th Annual American Cancer Society Nursing Research meeting, Newport Beach, CA.
- 2/99 Sick and tired of being tired and sick. Dimensions of cancer-related fatigue and its management, New Orleans, LA.
- 2/99 Management strategies for cancer-treatment-related fatigue. Dimensions of cancer-related fatigue and its management. New Orleans, LA.
- 1/99 Cancer-related fatigue: We can make a difference. Oregon Oncology Nursing Society, Portland, Or.
- 12/98 Keeping your energy up! Strategies for fatigue management. Melanoma support group, Group Health, Seattle, WA.
- 6/98 Energy expenditure and exercise adherence in women with breast cancer receiving chemotherapy. Poster presented at American College of Sports Medicine meeting, Orlando, FL.
- 5/98 Effects of exercise on the pattern of daily fatigue in women with breast cancer. Oncology Nursing Society Congress, San Francisco, CA.
- 3/98 Fatigue problems among athletic cancer survivors. NCI: Research Issues in Cancer Survivorship meeting, Bethesda, MD.
- 3/98 Exercise and Cancer, radio interview WBAI, New York City.
- 11/97 Relationship of exercise to fatigue and quality of life in women with breast cancer." Podium and poster presentation Department of Defense Era of Hope Breast Cancer Meeting, Washington, DC.

Peer reviewed publications resulting from this support:

Schwartz, A.L. (in press). Fatigue mediates the effect of exercise on quality of life in women with breast cancer. *Quality of Life Research*.

Schwartz, A.L., Nail, L.M., Chen, S.L., Meek, P., Barsevick, A.M., King, M.E., & Jones, L.S. (in press). Fatigue patterns observed in patients receiving chemotherapy and radiotherapy. *Cancer Investigation*.

Schwartz, A.L. Mori, T., Gau, R., Nail, L.M., King, M.E., Madsen, S. (in review). Exercise and fatigue: Day-to-day variation. *Nursing Research*.

Schwartz, A. L. (in review). Effect of exercise on weight gain in women with breast cancer receiving adjuvant chemotherapy. *Breast Cancer Res Treat*

Schwartz, A.L. (in review). Daily Fatigue Pattern and effect of exercise in women with breast cancer. *Cancer Nursing*

Published abstracts resulting from this support:

Schwartz, A.L. (1999). Effect of exercise on weight gain in women with breast cancer receiving adjuvant chemotherapy. *J. Clinical Oncology*,

Schwartz, A.L., Mori, M., & Nail, L.M. (1999). Exercise dose and daily pattern of fatigue. *Oncology Nursing Forum*, 26, 240.

Schwartz, A.L. (1999). Differences in the pattern of cancer-related fatigue and vigor. *Communicating Nursing Research Conference Proceedings*, 32, 125.

Schwartz, A.L., Mori, M., & Nail, L.M. (1999). Exercise dose and daily pattern of fatigue. *Proceedings of the 5th Annual American Cancer Society Nursing Research meeting*, Newport Beach, CA.

Schwartz, A.L. (1998). Effect of exercise on side effects, affect, and weight changes experienced by breast cancer patients receiving chemotherapy. *Proceedings of the American Society of Clinical Oncology meeting*, Los Angeles, CA.

Schwartz, A.L. (1998). Energy expenditure and exercise adherence in women with breast cancer receiving chemotherapy. *Medicine & Science in Sports & Exercise*, 30, S902.

Schwartz, A.L. (1998). Effect of exercise on the pattern of daily fatigue in women with breast cancer. *Oncology Nursing Forum*, 25, 310.

Schwartz, A.L. (1997). Effect of exercise on fatigue and quality of life in women with breast cancer. *Proceedings of the Department of Defense: Era of Hope Breast Cancer Conference*, Washington, D.C., November.

Awards resulting from this support:

1998 NIH R-29: Cancer, Catabolic Steroids, Exercise and Quality of Life (\$350,00)

1998 Outstanding Doctoral Dissertation Award, University of Utah, College of Nursing.

Proposals Pending

1999 NIH R-01 Breast Cancer Survivors: Exercise and Raloxifene (Priority Score: 110, Percentile 0.2).

Fatigue mediates the effect of exercise on quality of life
in women with breast cancer.
Quality of Life Research.



Fatigue mediates the effects of exercise on quality of life

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Accepted in revised form ■

Abstract. *Purpose:* Fatigue is a common side effect of cancer treatment that impacts quality of life. Exercise is one approach suggested to improve fatigue. The purpose of this study was to explore the relationship of exercise to fatigue and quality of life. *Methods:* Thirty-one subjects with breast cancer were enrolled prior to beginning chemotherapy and 27 completed the study. All baseline measures were obtained before the first chemotherapy treatment. Subjects were instructed on a home-based, 8-week exercise program. *Results:* Women who adopted the exercise program (60%) showed significant increases in functional ability and less weight gain. Exploratory, stepwise multiple regression analyses suggested

that the maximum effect of exercise on quality of life outcomes may be mediated by fatigue. *Conclusions:* The low-to-moderate intensity, home-based exercise program was feasible for some women with breast cancer receiving chemotherapy. The results suggest that exercise may affect quality of life and that this effect may be mediated by the effects of exercise on fatigue. Better retention of functional ability and better weight control are additional possible benefits of exposing breast cancer patients to increased exercise. A randomized, controlled clinical trial is needed to establish confidence in these observed relationships.

Key words: ■

Introduction

Fatigue is recognized as a common side effect of cancer treatment. The symptom is experienced by the majority (40–100%) of cancer patients regardless of diagnosis, stage of disease or type of treatment [1–3]. Although fatigue has been associated with inadequate nutrition, sleep, disease-related biochemical changes, reduced levels of activity and psychosocial factors, the aetiology of cancer treatment-related fatigue remains unclear [4–9]. Previous studies have demonstrated that fatigue affects cognition, reduces functional ability and impairs one's ability to interact with family and friends [10–14].

The common advice given to patients to limit their activities and rest may actually accelerate the declines in functional ability observed in patients receiving chemotherapy. Prolonged periods of bedrest and inactivity contribute to deconditioning and may contribute to fatigue [15]. Contrary to the usual advice to rest given to a patient, exercise is an intervention suggested to prevent cancer treatment-related fatigue [9, 16]. A small pilot study ($N = 5$) of cancer patients with diverse diagnoses suggested that aerobic exercise was a potential treatment for cancer fatigue, however it was unclear how fatigue was measured [17]. There is evidence to suggest that exercise decreases the physical and psychological side-effects of treatment and may help retard or prevent disease of disuse [18, 19]. Maintaining functional ability may slow the cycle

of disuse that builds up from treatment side effects and results in progressive physical debilitation, marked weakness and easy fatigability [2, 20–22]. The constellation of symptoms associated with disuse (increased fatigue, loss of self-esteem, inability to perform activities of daily living, loss of social relationships, and impaired work performance) have a negative effect on patients' quality of life [11, 13, 14, 23].

The purpose of this study was to examine the relationship of exercise to fatigue and quality of life. It was hypothesized that exercise would reduce fatigue and improve quality of life. Fatigue was proposed to be the mechanism through which exercise would affect quality of life, thus the mediating variable (Figure 1).

Design and intervention

A pretest–posttest, one-group design was used in this study. This design was selected because of the potential problems inherent in random assignment to a self-administered treatment which may be viewed as socially desirable. Subjects assigned to the control group may compensate by imitating the treatment on their own; seeking information and assistance from members of the experimental group; inflating self-reports of physical ability; dropping out of the study or allowing dissatisfaction with



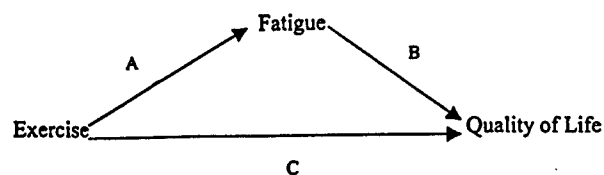


Figure 1. Mediating hypothesis tested.

their group assignment to influence quality of life ratings [24].

All subjects received instruction for the exercise program. The intervention was an 8-week, home-based, low-to-moderate intensity exercise program that allowed for periods of recovery and accommodated to individual cycles of chemotherapy by reducing the duration of exercise. Subjects were instructed to choose an aerobic activity that they enjoyed and to exercise between 15 and 30 min, 3 to 4 days a week. Subjects were instructed to exercise at an intensity that did not provoke or intensify their symptoms and to reduce their exercise intensity or stop the activity if their symptoms did not subside. Subjects received written guidelines for exercises that included instructions about exercise precautions and times to avoid exercise (e.g. immediately after chemotherapy, hematocrit <25%). A research assistant contacted the subjects each week to re-administer the measures and inquire about subjects' ability to exercise. Subjects were asked to begin the exercise program the week following the first cycle of chemotherapy. Variance in the level of exercise occurred as a result of subjects adopting the program at different levels. Data were collected on individual factors known to influence the decision to exercise (e.g. previous exercise history) in an attempt to address self-selection as a threat to the validity of the study.

Sample and method

All eligible women were invited to participate: newly diagnosed women with breast cancer, ambulatory, and documented radiotherapy and chemotherapy na, over 18 years old, and without musculoskeletal diseases that would preclude exercise. Potential subjects were enrolled before their first cycle of chemotherapy. Over a 10-months time period, 35 eligible women were identified from a private practice and university-based cancer clinic and 31 entered the study. Four women declined to participate for reasons related to being too busy. The final sample size was 27; 4 of the 31 subjects were either lost to follow-up ($n = 1$), withdrew from the study because of illness of another family member ($n = 1$), or were too busy ($n = 2$). The repeated measures design provided a power of greater than 0.83 ($R^2 = 0.25$, $\alpha = 0.05$) for a two-tailed test to detect the effect of level of exercise on cancer-related fatigue and quality of life.

Instruments

The 12-min walk measures the distance in feet an individual can walk in 12-min on a level surface in a controlled climate [25]. This test is used extensively in cardiovascular rehabilitation programs as a measure of improvement in functional ability after exercise rehabilitation [26] and is highly correlated ($r = 0.9$) with laboratory oxygen consumption tests [25]. This test, administered at baseline and posttest, was used to measure functional ability and reflected adherence to the exercise program. All subjects received the same instruction before the test, a 5-sec countdown to begin and received encouragement only in the final 2 min of the walk.

CaltracTM accelerometer (Muscle Dynamics Fitness Network: Torrance, CA, USA) monitoring was used to assess energy expenditure. This instrument is worn on the waistband and records cumulative movement. An algorithm that takes into account activity, gender, height, weight, and age is used to estimate calories expended. It is highly reliable and related to oxygen consumption of 14 activities at a range of different intensities [27-29]. Subjects were instructed to use the CaltracTM with each exercise session and maintain a record of calories expended to determine exercise intensity. Verbal and written instruction was provided on how to use the CaltracTM accelerometer, maintain the exercise log and contact the investigator if there were problems with the CaltracTM. Body weight was also recorded before each cycle of chemotherapy.

Cancer-related fatigue was measured once a week with two scales. The fatigue-inertia and vigor-activity subscales from the Profile of Mood States (POMS) was one measure [30]. The POMS is a well established instrument that was developed to measure mood [30]. Scores on these subscales range from 0 to 32 on the 8-item fatigue subscale, and 0 to 28 on the 7-item vigor subscale; both are measured on a 0 to 4 point scale with lower scores representing less fatigue and less vigor, respectively. Internal consistency reliabilities are 0.94 for fatigue-inertia and 0.89 for vigor-activity.

The second weekly measure was the Schwartz Cancer Fatigue Scale (SCFS). The 6-item SCFS was selected because it is not a measure of mood, but developed to specifically measure cancer-related fatigue on a physical and perceptual dimension. Total scale scores range from 6 to 30 using 1 = not at all to 5 = extremely scale for each item. Lower scores represent less fatigue. Cronbach's α , a measure of internal consistency reliability, for the total scale ($\alpha = 0.90$) and subscales (physical = 0.88, perceptual subscale = 0.81) was strong. The scale has demonstrated construct validity with both exploratory and confirmatory factor analysis in people with cancer [31, 32]. The SCFS has demonstrated sensitivity ($p < 0.001$) and construct validity with the Profile of Mood States fatigue subscale, Lee Fatigue

Scale, Multidimensional Fatigue Inventory, and the Multidimensional Assessment of Fatigue ($p < 0.001$ for all scales). The SCFS discriminates between subjects receiving treatment and those who completed treatment ($p < 0.01$) [31]. Both the POMS and SCFS were measured at weekly intervals.

In addition to the weekly measures, subjects recorded daily measures of fatigue on 100 mm visual analogue scales (VAS-F). Subjects were asked to place a mark on the horizontal line that represented their worst and average fatigue in the past 24 hours. To improve consistency of the measure and help subjects remember to complete the measure, subjects were asked to place a mark on the lines at the same time each night before going to bed. Variance scores of the worst and average daily VAS-F were used to capture the pattern of fatigue over the study period from baseline to posttest. Visual analogue scales are commonly used to assess fatigue in cancer patients [31, 33].

The 23-item version of the Quality of Life Index for patients with cancer was used to measure the multidimensional aspects of quality of life [34]. Four of the items were modified to be breast cancer specific. Scores on the Quality of Life Index range from 0 to 100, with higher scores denoting a higher quality of life. The total scale has a reported Cronbach's α of 0.88 [34] and has demonstrated construct and discriminate validity. The modified version used in this study had a Cronbach's α of 0.85. Quality of life was measured at baseline and posttest.

Side Effect Symptom Checklist was also used to monitor number and severity of side effects experienced each week. The instrument was developed for use with cancer patients and consists of 11 symptoms commonly associated with chemotherapy [35]. Symptoms are rated on a 0 = not present to 5 = extremely severe scale. Internal consistency reliability has not been reported, but different and unrelated symptoms are being measured, so it is neither expected nor critical that there be a high level of internal consistency [36].

Procedure

The study was explained, written informed consent was obtained and pre-intervention baseline measures were collected. Baseline measures were obtained before the subject received her first dose of chemotherapy. At baseline, all subjects completed a demographic questionnaire, 12-min walk, Profile of Mood States subscales (vigor-activity and fatigue-inertia), Schwartz Cancer Fatigue Scale, Visual Analogue Scales of worst and average fatigue, the Quality of Life Index for patients with cancer, and Side Effect Symptom Checklist. Clinical information was also obtained at this time (e.g. disease history, chemotherapy regimen, body weight). Subjects

maintained an exercise log of duration and type of exercise, and energy expenditure measured with a CaltracTM accelerometer, and a fatigue log of daily worst and average fatigue. A research assistant telephoned subjects every week to re-administer the Profile of Mood States vigor and fatigue subscales, Schwartz Cancer Fatigue Scale and Side Effect Symptom Checklist; subjects were reminded to mail their exercise and fatigue logs to the study center. The weekly telephone contact served as a means to inquire about subjects' ability to exercise and for those subjects who adopted exercise, provided reinforcement to adhere to the exercise program. No subject was admonished for not exercising. Posttest measures were obtained on all measures, except demographics, 1 to 2 days before receiving the fourth cycle of chemotherapy.

Preliminary analyses

Descriptive analyses were used to describe the sample, adherence to the exercise program, level of exercise, fatigue levels, side effects and overall quality of life measures. Standard cohort χ^2 tests and t -tests were used to compare subjects who dropped out with those who completed the study on baseline measures and presence of adverse events due to cancer treatment or exercise. The worst and average daily VAS-F data for each subject was extremely variable. As a means of capturing the swings in fatigue over time variance scores of the worst and average daily VAS-F were used to examine the relationship of daily fatigue to level of exercise. VAS-F variance scores were used in the multiple regression analysis and analysis of variance. To obtain the variance score for each subject, the sum of squares was divided by the number of scores available for each variable.

Posttest percentage of baseline 12-min walk distance, the measure of functional ability, was calculated by dividing the posttest distance by the baseline distance and multiplying by 100. Subjects whose scores were greater than 100% (indicating an increase in distance walked) were defined as having increased their functional ability. Exercise intensity was calculated by dividing the total number of minutes exercised over the 8-week study period by the total CaltracTM accelerometer. This score provided a quantification of the intensity of exercise that each subject engaged in during the study period. Although not all women improved in functional ability, all women recorded some exercise during the study period and had a score for exercise intensity.

Tests of the mediating hypothesis were examined using the classic techniques described by Baron and Kenny [37], and Lindley and Walker [38]. Four regression equations were used to test the links in the model: (a) level of exercise was regressed on quality of life (path C_1 , Figure 2); (b) fatigue was regressed on

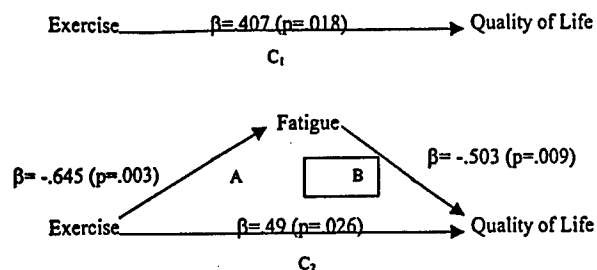


Figure 2. Mediating effects of fatigue.

level of exercise (path A); (c) quality of life was regressed on fatigue (path B); and (d) quality of life was regressed on exercise and fatigue (path C₂). To establish a mediating effect three conditions must be met: (a) level of exercise must influence the mediator, fatigue; (b) fatigue must significantly affect quality of life; and (c) if the preceding conditions held in the expected direction, then the effect of level of exercise must decrease in the final regression. The strongest example of mediation occurs when the independent variable (level of exercise) has no effect, when the mediator (fatigue) is controlled.

Stepwise regression procedures were used to test the effects of level of exercise on the worst and average daily VAS-F. Criteria for retention were set at PIN = 0.05 and POUT = 0.10. The dependent variables were variance in worst and average fatigue and were entered in separate analyses. Independent variables were entered in the following order: functional ability, exercise intensity, age, and baseline worst and average fatigue. Differences in the worst and average daily VAS-F by type of chemotherapy and stage of disease were examined using one-way analysis of variance. Hierarchical analysis, holding baseline quality of life constant, was employed to determine the unique effect of level of exercise to quality of life.

Results

All results, except demographic data, are reported on the 27 subjects who completed the study. There were no significant differences in demographic characteristics, baseline measures, or frequency of adverse events (e.g. neutropenic fever) between those who completed the study and the 4 who did not. The sample ranged in age from 35–57 (mean age = 47 years). The majority of the sample were married (74.2%), Caucasian (87.1%), had attended some college (77.5%) and were employed full-time (54.8%). All subjects had surgery at least 21 days prior to beginning treatment with chemotherapy. In this sample, 7 (23%) women had stage I breast cancer and were receiving cyclophosphamide, methotrexate and fluorouracil (23.3%), and 22 (73%) women had stage II or III disease and were being treated with cyclophosphamide and doxorubicin. One woman was

being treated for stage IV breast cancer with liver metastasis and was receiving vinorelbine.

More than half of the subjects (54.8%) did not exercise regularly prior to entering the study. Subjects who participated in regular exercise before entering the study reported spending an average of 42 min per exercise session (SD = 16.6) and exercised on the average 4 days per week (SD = 1.5). At baseline walking was the most popular activity for 23.3% of exercisers, followed by aerobics classes, bicycling, and golf. Results indicated that 60% of the sample adopted the exercise program and received a training benefit as measured by increased functional ability. These women all reported walking as their primary activity with some also engaging in weight lifting, aerobics classes, golf and snow skiing. Two subjects who were regular exercisers at baseline did not continue to exercise during the study.

Baseline mean functional ability, as measured by the 12-min walk, for the group was 3702.0 feet (SD = 474.7). Women who demonstrated increases in functional ability on the posttest 12-min walk and who reported data in the exercise logs were considered to have benefited from and adopted the exercise program. There were no differences ($t = -0.53$, $p = 0.60$) in baseline functional ability between subjects who adopted exercise ($M = 3714.1$, $SD = 545.6$) and those subjects who did not adopt the exercise program ($M = 3672.4$, $SD = 465.2$). Significant differences in functional ability were observed at posttest ($t = -3.6$, $p = 0.002$). Subjects who adopted exercise ($n = 16$) demonstrated a mean percent increase in functional ability of 10.4% (SD = 7.67%), while nonexercising subjects ($n = 11$) showed an average decline of nearly 16% (SD = 12.9%). At posttest, functional ability for subjects who adopted exercise ranged from 3324 to 5747 feet ($M = 4089$, $SD = 616.2$), and for subjects who did not adopt exercise ranged from 1763 to 3934 feet ($M = 3097$, $SD = 616.8$). In this study, subjects who adopted this intervention, exercised an average of 35 min per session (SD = 15), 4 days per week (SD = 1.2); expending an average of 182 calories per exercise session (SD = 100). Although many of the nonexercisers recorded exercise in their logs, they clearly did not exercise at an intensity or frequency to sustain improvements in functional ability.

Fatigue scores on both the POMS fatigue subscale and the SCFS were lowest at baseline and peaked after the third dose of chemotherapy (Chart 1). Vigor, measured by the POMS vigor subscale, was highest at baseline and lowest after the third chemotherapy treatment. Although the weekly measures of fatigue demonstrated change over time, the daily VAS-F scores exemplified the extreme variability and instability of fatigue. Subjects' scores utilized the full range of the VAS-F.

Quality of life was measured at baseline ($M = 61.4$, $SD = 10.9$) and posttest ($M = 56.8$,

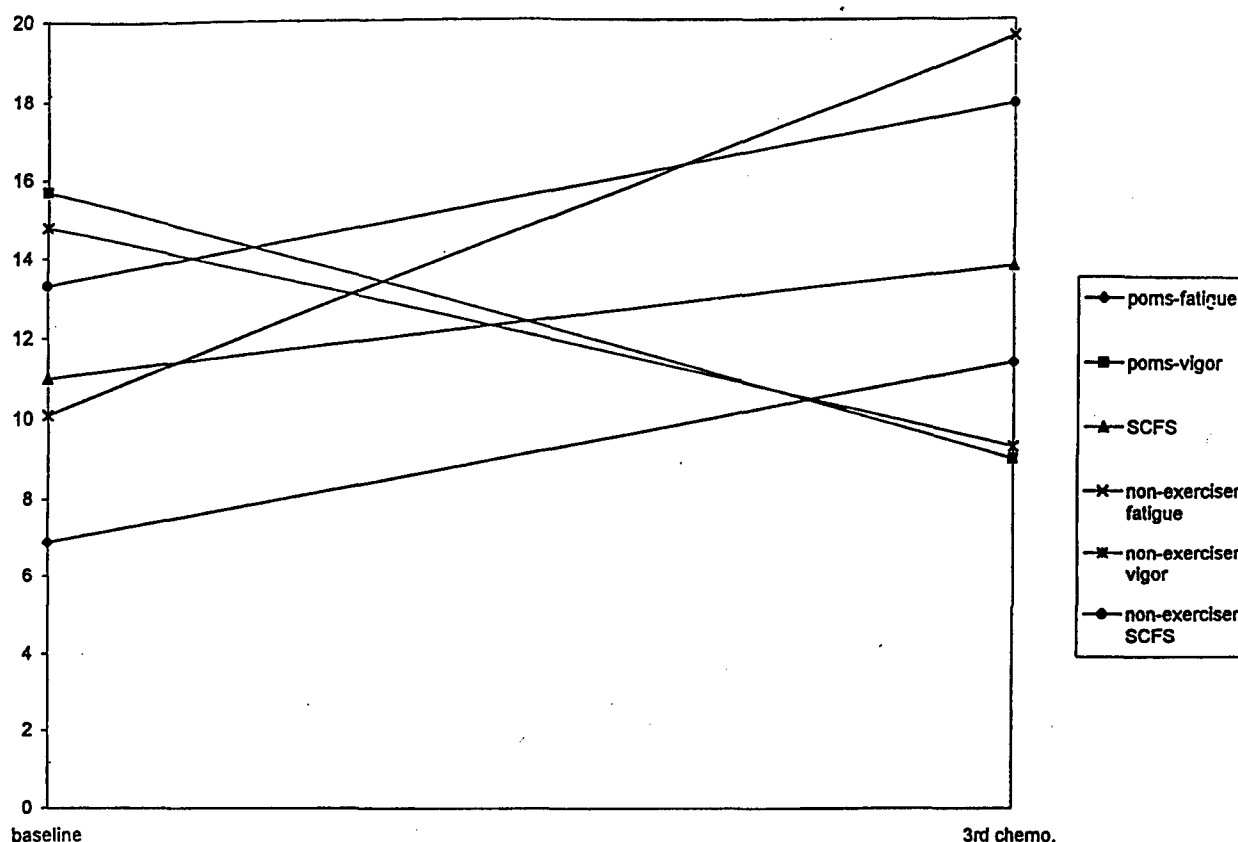


Chart 1. Peak and high fatigue and vigor scores for exercisers and non-exercisers at baseline and after third chemotherapy treatment.

SD = 10.5). Although quality of life declined for nearly all subjects, the subjects who improved in functional ability demonstrated less overall decline ($t = -2.1, p = 0.04$). The instruments used to measure the concepts fatigue and quality of life performed adequately with Cronbach's α exceeding 0.8 for all measures and demonstrating variability over time.

Side effects, measured on the Side Effect Symptom Checklist, Scores did not differ between exercisers and non-exercisers at baseline ($t = 1.2, p = 0.24$). While the exercises consistently demonstrated lower side effect scores at each weekly measure, the differences were not significant ($p > 0.05$). The most severe and common side effects experienced by both exercisers and nonexercisers at baseline were numbness in the arm on the treated side (mean intensity = 2.5; 77%), difficulty sleeping (mean intensity 1.9; 63%), pain (mean intensity = 1.8; 73%), and difficulty concentrating (mean intensity 1.5; 57%). At posttest the most common side effects were difficulty sleeping (mean intensity 1.9; 63%), difficulty concentrating (mean intensity 1.7; 67%), hot flashes (mean intensity 1.4; 44%), and numbness in the arm on the treated side (mean intensity = 1.3; 57%).

Differences in weight gain were observed over time. At baseline there were no differences between the exercisers and nonexercisers ($t = 1.6, p = 0.18$), but at posttest the exercisers had maintained or lost weight while the nonexercisers had gained weight

($t = 2.53, p = 0.03$). No differences were observed using simple analysis of variance to examine differences by type of chemotherapy for posttest measures of fatigue, side effects, functional ability or quality of life ($p > 0.30$).

Test of mediating hypothesis

In order to examine the mediating hypothesis, four regression equations were computed using standard techniques described by Baron and Kenny [37] and Lindley and Walker [36]. Following this technique, multiple regression, using stepwise analysis, was used to examine the relationship of level of exercise (functional ability and exercise intensity scores) to quality of life. To determine if fatigue was the mechanism (mediating variable) through which exercise affected quality of life the following four hypotheses were tested with the following results: (1) The first analysis examined the hypothesis that level of exercise, as measured by functional ability and exercise intensity, would be positively and significantly related to quality of life at posttest. This analysis tested the effects of quality of life on exercise (path C_1 , Figure 2). Nearly 56% of the variance in quality of life was explained by exercise ($p < 0.05$) (Table 1); justifying examination of the second hypothesis.

Table 1. Stepwise regression analysis of the effect of exercise on fatigue and quality of life (N = 27)

	R^2		p	β	Partial R^2	Signif p
	Combined	Individual				
Quality of life on Exercise	0.558		0.018			
Exercise intensity		0.206		-0.491	-0.564	0.044
Functional ability		0.352		0.407	0.493	0.018
Fatigue on Exercise	0.732		0.001			
Exercise intensity		0.379		0.365	0.344	0.039
Functional ability		0.353		-0.645	-0.535	0.003
Quality of life on Fatigue	0.709		0.018			
POMS ¹ -vigor		0.433		0.433	0.384	0.006
SCFS ² total		0.593		-0.503	-0.363	0.009
Quality of Life on Exercise and Fatigue ³	0.714		0.026			
SCFS total		0.575		-0.444	-0.537	0.039
POMS-vigor		0.140		0.488	0.573	0.026

¹ Profile of Mood States vigor subscale. ² Schwartz Cancer Fatigue Scale. ³ Level of exercise did not enter equation; accounting for 0 variance.

The second hypothesis predicted that level of exercise, as measured by functional ability and exercise intensity, would be negatively and significantly related to fatigue scores, measured by the SCFS, at posttest. Results of the regression analysis were significant (path A, Figure 2). Exercise intensity and functional ability when regressed on fatigue explained 73% of the variance in fatigue ($p < 0.01$) (Table 1); justifying examination of the second hypothesis.

The second hypothesis predicted that level of exercise, as measured by functional ability and exercise intensity, would be negatively and significantly related to fatigue scores, measured by the SCFS, at posttest. Results of the regression analysis were significant (path A, Figure 2). Exercise intensity and functional ability when regressed on fatigue explained 73% of the variance in fatigue ($p < 0.01$). This result supported proceeding with the next step in the analysis.

Hypothesis 3 predicted that fatigue, as measured by the SCFS and POMS, would be inversely and significantly related to quality of life at posttest. To test this relationship the effect of quality of life was regressed on fatigue (path B, Figure 2). In this regression equation fatigue accounted for nearly 71% of the variance in quality of life ($p < 0.05$). The final test of the linkages in the model was to examine hypothesis 4.

This final hypothesis proposed that when fatigue was entered into the analysis simultaneously with level of exercise, level of exercise would no longer be related to quality of life. Indeed, level of exercise failed to even enter the regression equation, contributing nothing to the variance in quality of life. This analysis demonstrated the strong mediating effect of fatigue (path C₂, Figure 2). Fatigue accounted for 71% of the variance in quality of life ($p < 0.05$), and

demonstrated a strong inverse relationship with quality of life. The decreases in fatigue observed in this sample appear to be caused by level of exercise, which in turn contributes to an improved quality of life.

Effect of level of exercise on fatigue

The effect of level of exercise on fatigue was tested by stepwise multiple regression analyses. Variance in the worst and average VAS-F scores was examined, in separate analyses, by functional ability, exercise intensity, age, and baseline worst and average VAS-F. Exercise intensity had a strong positive relationship with worst VAS-F ($R^2 = 0.55$, $p = 0.02$) and accounted for 30% of the variance. While this finding appears to contradict the mediating hypothesis, it suggests that: (1) there may be an optimal dose or intensity of exercise to reduce fatigue, (2) subjects who exercise at too high of an intensity may provoke fatigue, or (3) it may be a response to severe fatigue. An inverse relationship was observed in functional ability and average VAS-F ($R^2 = -0.49$, $p = 0.02$). This regression accounted for approximately 24% of the variance in average VAS-F. Subjects who adopted exercise increased their functional ability and experienced less variance in their average fatigue. Neither age nor baseline fatigue (worst or average) contributed to predicting who would adopt exercise.

Contribution of level of exercise to quality of life

To determine the unique effect of level of exercise to quality of life, hierarchical regression analysis was performed (holding baseline quality of life constant).

As expected, the contribution of level of exercise decreased, but was still significant ($R^2 = 0.62$, $p = 0.01$), explaining 23% of the variance in posttest quality of life. Simple analysis of variance failed to disconfirm the null hypothesis of no differences in level of exercise or fatigue related to either type of chemotherapy ($F = 0.06$, $df = 1$, $p = 0.81$ and $F = 0.07$, $df = 1$, $p = 0.79$, respectively) or stage of disease ($F = 1.63$, $df = 3$, $p = 0.21$, and $F = 0.39$, $df = 3$, $p = 0.76$, respectively). The trend was for lower levels of exercise among women with stage I breast cancer, but the trend was not sustained by post hoc comparisons ($p > 0.31$).

Discussion

The home-based, low-to-moderate intensity exercise program was feasible for some women with breast cancer receiving chemotherapy. Women who adopted the exercise program demonstrated less weight gain, improved functional ability, and quality of life. Also, women who exercised increased their functional ability, experienced less fatigue and increased vigor. Some of the women who did not adopt exercise reported shopping or routine housework as exercise. Although current physical activity recommendations recognize activities of daily living, such as, house cleaning and mowing the lawn, as important contributors to maintaining and improving health [39], the exercise intervention in this study was specifically defined as deliberate aerobic activity that was different from one's usual activities of daily living.

Although all subjects who did not adopt the exercise program showed declines in functional ability, the greatest declines were observed in two subjects who were regular exercisers at study entry. These two women began the exercise intervention but were unable to continue exercising when they developed infections. Both women were treated for infections that were managed on an outpatient basis. These women attributed their lack of exercise to their need to maintain family, work and social obligations. The substantial declines (22 and 36%, respectively) in functional ability observed in these subjects were remarkable for an 8-week period. The declines in functional ability of these women raise concerns about the extent to which regular exercisers are encouraged to continue exercising during cancer treatment. Women who are regular exercisers before diagnosis may be at an increased risk for dramatic declines in functional ability with cessation of exercise during chemotherapy. The rapid declines in functional ability in these women suggest the importance of regular exercise to maintain or retard functional ability declines. While it could be argued that these women did not exercise because of their treatment-related fatigue, it should be noted that

these women were exercising until their infections developed. Therefore, it seems more likely that the fatigue from their infections coupled with cancer treatment-related fatigue posed too great a barrier to exercise.

The home-based approach to exercise was well liked by subjects, as nearly 60% of the sample adhered to the exercise program; exceeding the adherence rate observed in most structured exercise programs for healthy, middle-aged persons [40]. Similar to findings from studies of subjects in health maintenance and rehabilitation programs, women in this home-based exercise program adhered to the exercise prescription and were given the freedom to exercise when it was convenient and when they felt best [39–42]. An ongoing challenge is determining how to motivate subjects who did not adopt the program. A serendipitous observation was that the women enjoyed using the CaltracTM accelerometers and found the devices to be motivating. Reasons for noncompliance were: (1) needing a more structured and supervised exercise program, (2) being too busy, and (3) lacking self-discipline. At baseline, all of the women who enrolled in the study intended to follow the exercise program, although some were less confident they would succeed than others. The majority of women cited the diagnosis of breast cancer and being part of an exercise study as reasons that would motivate them to adhere to the exercise program as well as make other positive lifestyle changes. Patients who do not have an interest in exercise may be motivated to begin an exercise program if they are educated about the potential positive effects on fatigue, functional ability and quality of life. These patients may benefit from a more structured, supervised exercise program. As more evidence supports the benefits of exercise in the treatment and rehabilitation phases of cancer care [17, 20–22], more women may choose or be instructed to exercise by their health care providers.

In this small sample of newly diagnosed women with breast cancer, fatigue appears to be the mechanism through which exercise affects quality of life – by decreasing fatigue, exercise improves quality of life. The findings of this study suggest that the usual advice given to patients to rest and limit physical activity during cancer treatment and in the immediate period following treatment may not be in the best interest of the patient. In fact, this well-meaning advice may cause muscle weakness and loss of functional ability. Furthermore, lack of exercise may directly contribute to increased fatigue and declines in quality of life during and following treatment [17, 21, 22, 43]. These findings are timely given the current increasing clinical interest in exercise to reduce fatigue [44].

A U-shaped relationship between high intensity exercise and fatigue was observed in this study; both nonexercisers and heavy exercisers (high intensity

and/or long duration) reported increased fatigue. Although this finding appears to contradict the mediating hypothesis, it supports the idea that there may be an optimal dose (intensity, frequency or duration) of exercise. These preliminary results suggest that exercise has a positive effect on fatigue and quality of life during chemotherapy, but that overextending or overexerting may cause increased fatigue. Exercise prescriptions may need to be individualized according to patients' functional ability and maintained at a level that does not induce fatigue.

This and other studies [16, 20-22, 33] suggest the need for cancer rehabilitation programs during and after cancer treatment. As cancer treatment becomes more effective, many patients are living long and productive lives as cancer survivors. The number of cancer survivors makes it increasingly important to maintain the functional ability of cancer patients during and after cancer treatment. Like their healthy counterparts, cancer survivors who follow a physically active lifestyle should be able to appreciate the protective benefits of exercise: reduced risk of coronary heart disease, hypertension, non-insulin-dependent diabetes mellitus, osteoporosis, colon cancer, anxiety and depression [45, 46].

Despite the small sample, the prescribed home-based exercise intervention had several positive effects on health (reduced fatigue, improved functional ability and quality of life) that have been observed in other studies with cancer patients [16, 17, 20-22, 33] and patients with chronic diseases [46]. Exercise appears to help patients retain their ability to continue with activities they see as important [47, 48]. It also improves patients' resiliency and overall quality of life both during and after treatment [20-22, 47]. Of course, self-selection bias may have influenced which patients in this study elected to adopt exercise and may have strongly affected these results. However, similar improvements in health behaviors and health status were observed in a randomized self-management intervention to improve the health status of patients with chronic disease [47].

In spite of the challenges of conducting a randomized clinical trial with an intervention that may be viewed as desirable, research using this design is needed to identify the optimal dose of exercise to reduce fatigue, determine the optimal time to exercise to minimize the onset and duration of fatigue after chemotherapy, and minimize the bias inherent in this study. Even though the best predictor of future exercise is past exercise behavior [45, 50], the diagnosis of breast cancer is life changing. It is conceivable that effective interventions may be developed to motivate newly diagnosed patients to become regular exercisers [47]. Effective interventions may build on or combine the ideas of the social support theory or Self-Efficacy Theory [50, 51] to promote behavior change or on the perceived susceptibility to illness posited by

the health belief model [52]. Although the single group design and small sample size limits generalizability, the results provide preliminary support for home-based, low-to-moderate intensity exercise programs as an intervention to decrease fatigue, control body weight and improve quality of life in women with breast cancer.

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References

1. Irvine D, Vincent L, Graydon JE, Bubela N, Thompson L. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. *Cancer Nursing* 1994; 17: 367-378.
2. Nail LM, Winningham ML. Fatigue and weakness in cancer patients: The symptom experience. *Sem Oncol Nursing* 1995; 11: 272-278.
3. Richardson A, Ream E, Wilson-Barnett J. Fatigue in patients receiving chemotherapy: Patterns of changes. *Cancer Nursing* 1998; 21: 17-30.
4. Aistars J. Fatigue in the cancer patient: A conceptual approach to a clinical problem. *Oncol Nursing Forum* 1987; 12: 122-127.
5. Bruera E, MacDonald RN. Asthenia in patients with advanced cancer. *J Symptom Manag* 1988; 3: 9-14.
6. Piper BF, Lindsey AM, Dodd MJ. Fatigue mechanisms in cancer patients: Developing nursing theory. *Oncol Nursing Forum* 1987; 14: 17-23.
7. St. Pierre BA, Kasper CE, Lindsey AM. Fatigue mechanisms in patients with cancer: Effects of tumor necrosis factor and exercise on skeletal muscle. *Oncol Nursing Forum* 1992; 19: 419-425.
8. Smets EMA, Garssen B, Schuster-Utterhoeve ALJ, et al. Fatigue in cancer patients. *British J Cancer* 1993; 68: 220-224.
9. Winningham ML, Nail LM, Burke MB, Brophy L, Cimprich B, Jones LS, et al. Fatigue and the cancer experience: The state of the knowledge. *Oncol Nursing Forum* 1994; 21: 23-36.
10. Cimprich B. Attentional fatigue following breast cancer surgery. *Res Nursing and Health* 1992; 15: 199-207.
11. Pickard-Holley S. Fatigue in cancer patients. *Cancer Nursing* 1991; 14: 13-19.
12. Post-White J, Schroeder L. Factors influencing breast cancer survivors' fatigue, emotional state and immune function and quality of life. *Proceeds from the American Cancer Society National Conference on Cancer Nursing Research*, Panama City, FL, January 1997.
13. Rhodes VA, Watson PM, Hanson BM. Patient descriptors of the influence of tiredness and weakness on self-care. *Cancer Nursing* 1992; 11: 186-194.
14. Skalla KA, Lacasse C. Patient education for fatigue. *Oncol Nursing Forum* 1992; 19: 1537-1539.

15. Galantino ML. Performance status = Nutrition + Exercise. *Nutritional Oncol* 1995; 2: 1-12.
16. MacVicar MG, Winningham ML. Promoting the functional capacity of cancer patients. *Cancer Bulletin* 1986; 38: 235-239.
17. Dimeo F, Rumberger BG, Keul J. Aerobic exercise as therapy for cancer fatigue. *Med Sci Sports and Exerc* 1998; 30: 475-478.
18. Shangraw RE, Stuart CA, Prince MJ. Insulin responsiveness of protein metabolism in vivo following bed rest in humans. *Am J Physiol* 1988; 255: E548-E558.
19. Stuart CS, Shangraw RE, Prince MJ. Bed-rest induced insulin resistance occurs primarily in muscle. *Metabolism* 1988; 37: 802-806.
20. Mock V, Dow KH, Meares CJ, Grimm PM, Dienemann JA, Haisfield-Wolfe ME, et al. An exercise intervention for management of fatigue and emotional distress during radiotherapy treatment for breast cancer. *Oncol Nursing Forum* 1997; 24: 991-1000.
21. Dimeo FC, Tilmann MHM, Bertz H, Kanz L, Mertelsmann R, Keul J. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous stem cell transplantation. *Cancer* 1997; 79: 1717-1722.
22. Dimeo FC, Fetscher S, Lange W, Mertelsmann R, Keul J. Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood* 1997; 90: 3390-3394.
23. Young-McCaughan S, Séxton DL. A retrospective investigation of the relationship between aerobic exercise and quality of life in women with breast cancer. *Oncol Nursing Forum* 1991; 18: 751-757.
24. Cook TD, Campbell DT. Quasi-experimentation: Design and analysis issues for field settings. Boston: Houghton Mifflin Company, 1979: 50-55.
25. Cooper KH. A means of assessing maximal oxygen uptake. *J Am Med Assoc* 1968; 203: 133-138.
26. Steele B. Timed walking tests of exercise capacity in chronic cardiopulmonary illness. *J Cardiopulmonary Rehab* 1996; 16: 25-33.
27. Montoye HJ, Washburn R, Seavers S, Eritt A, Webster A, Nagle F. Estimation of energy expenditure by portable accelerometer. *Med Sci Sports and Exerc* 1983; 15: 899-907.
28. Sallis JF, Buono MJ, Roby JJ, Carlson D, Nelson JA. The Caltrac accelerometer as a physical activity monitor for school-age children. *Med Sci Sports and Exerc* 1990; 22: 698-703.
29. Washburn RA, LaPorte RE. Assessment of walking behavior: Effect of speed and monitor position on two objective physical activity monitors. *Res Quart Exerc and Sports* 1988; 59: 83-85.
30. McNair DM, Lorr M, Droppelman LF. Profile of mood states manual. San Diego: Educational and Industrial Testing Service, 1992: 16-18.
31. Schwartz AL. Reliability and validity of the Schwartz Cancer Fatigue Scale. *Oncol Nursing Forum* 1998; 25: 711-717.
32. Schwartz AL, Meek P. Additional construct validity of the Schwartz Cancer Fatigue Scale. *J Nursing Measur* 1999; in press.
33. Mock V, Burke MB, Sheehan P, Creaton EM, Winningham ML, McKenney-Tedder S, et al. A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. *Oncol Nursing Forum* 1994; 21: 899-907.
34. Padilla GV, Grant MM. Quality of life as a cancer nursing outcome variable. *Adv Nursing Sci* 1985; 8: 45-60.
35. King KB, Nail LM, Kraemer K, Strohl R, Johnson J. Patients' descriptions of the experience of receiving radiation therapy. *Oncol Nursing Forum* 1985; 12: 55-61.
36. Nunnally JC, Bernstein IH. *Psychometric Theory*, 3rd ed. New York, NY: McGraw Hill, 1994.
37. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical considerations. *J Personality and Social Psychol* 1986; 51: 1173-1182.
38. Lindley P, Walker SN. Theoretical and methodological differentiation of moderation and meditation. *Nursing Res* 1993; 42: 276-279.
39. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *J Am Med Assoc* 1995; 22: 402-407.
40. Dishman RK. Determinants of participation in physical activity. In: Bouchard C, Shepard RJ, Stephens T, Sutton JR, McPherson BD. *Exercise, Fitness and Health: A consensus of current knowledge*. Champaign, IL: Human Kinetics Publishers, 1990: 78-101.
41. King AC. Community and public health approaches to the promotion of physical activity. *Med Sci Sport and Exerc* 1994; 26: 1405-1412.
42. King AC, Haskell WL, Taylor B, Kraemer HC, DeBusk RF. Group- vs home-based exercise training in healthy older men and women: A community based clinical trial. *JAMA* 1991; 266: 1535-1542.
43. King AC, Young DR, Oka RK, Haskell WL. Effects of exercise format and intensity on two-year health outcomes in the aging adults (Abstract). *The Gerontologist* 1992; 32: 190.
44. News section. Tired out Patients find few easy answers for cancer-related fatigue. *J Nat Cancer Inst* 1998; Nov4: 1591.
45. McAuley E, Courneya KS, Rudolph DL, Lox CLL. Enhancing exercise adherence in middle-aged males and females. *Prev Med* 1994; 23: 498-506.
46. Christensen T, Stage JG, Glabo H, Christensen NJ, Kehlet H, et al. Fatigue and cardiac and endocrine metabolic response to exercise after abdominal surgery. *Surgery* 1989; 105: 46-50.
47. Lorig KR, Sobel DS, Stewart AL, Brown BW, Bandura A, Ritter P, Gonzalez VM, Laurent DD, Holman HR. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization. A randomized trial. *Med Care* 1999; 37: 5-14.
48. Schwartz AL. Patterns of exercise and fatigue in physically active cancer survivors. *Oncol Nursing Forum* 1998; 25: 485-491.
49. Pate PR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American college of Sports Medicine. *JAMA* 1995; 273: 402-407.

50. Eaton CB, Reynes J, Assaf AR, Feldman H, Lasater T, Carlton RA. Predicting physical activity change in men and women in two New England communities. *Am J Prev Med* 1993; 9: 209-219.
51. Broadhead WE, Kaplan BH, James, et al. The epidemiologic evidence for a relationship between social support and health. *Am J Epidemiol* 1983; 117: 521-537.
52. Rosenstock IM. The health belief model and preventive health behavior. *Health Educ Monogr* 1974; 2: 354-386.

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Fatigue patterns observed in patients receiving chemotherapy and radiotherapy.
Cancer Investigation.

Fatigue Patterns Observed in Patients Receiving Chemotherapy and Radiotherapy

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RUNNING HEAD: Patterns of Fatigue

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Abstract:

The purpose of this study was to describe the patterns of cancer-related fatigue (CRF) and vigor in patients receiving chemotherapy or radiation therapy. Five studies that measured fatigue and vigor with the Profile of Mood States were used to describe the pattern of CRF and vigor during and after both types of treatment. Repeated measures analysis of variance was used to determine differences over time in each of the studies. Results demonstrate different patterns of CRF for patients receiving chemotherapy and radiation therapy. Chemotherapy related CRF peaks in the days following chemotherapy, whereas radiation therapy related CRF gradually accumulates over the course of treatment. The CRF associated with both forms of treatment gradually declines over time. The prevalence, intensity and persistence of CRF during treatment and for months after treatment is complete make this symptom one that can not be ignored.

Fatigue Patterns Observed in Patients Receiving Chemotherapy and Radiotherapy

The relentless and intense nature of cancer-related fatigue makes it distinctly different from the fatigue experienced by healthy individuals. Cancer-related fatigue (CRF) is the most intense, distressing and prolonged side effect of cancer treatment (1-3) with the incidence reported to effect between 59 and 100% of patients (3-7). Patients describe CRF as distinctly different, a more severe and unpredictable type of fatigue, than the fatigue they experienced before receiving either chemotherapy or radiotherapy (8-9). Patients often misinterpret CRF as advancing disease or failure to respond to treatment and worry about reporting the symptom to their physician who may tell the patient that s/he does not look especially tired. CRF is not only a highly prevalent and distressing symptom, but also a symptom that lingers years after patients have completed treatment (9, 10).

Differences in the incidence and severity of CRF have been noted by age, gender, stage of disease, and functional ability. These differences should be interpreted with caution since the effects of different types of disease, and treatment protocols on the incidence and severity of CRF are unknown. Older age tends to confer less intense CRF in patients receiving both chemotherapy and radiotherapy (11-13) and the experience of CRF is believed to be less distressing for older patients (14). Although no studies have prospectively examined gender differences in CRF, males are noted to have lower fatigue scores than females. The etiology of this finding may reflect the types of cancer and other treatment related variables that differentially affect men and women (15). Treatment outcomes have long been associated with functional ability. Low performance status and the presence of metastatic disease are also predictive of higher CRF scores (13, 15, 16).

The numerous variables that influence the severity of this symptom make individual patient management complex.

CRF is a frustrating symptom for clinicians; little is understood about the mechanism; few interventions have demonstrated efficacy; and much debate surrounds the optimal way to define the concept. Knowledge of the pattern of CRF is needed to guide the timing of clinical assessment, provide information to patients about the expected onset and duration of CRF, aid patients in planning energy conservation strategies, and support clinicians in identifying peaks in CRF and unexpected changes in baseline levels.

However, developing an awareness of the significance of the symptom, being able to describe the pattern of CRF to patients and helping patients to understand what they should expect is a small first step in tackling this troubling symptom. We report the results of five studies that examine the pattern of CRF in patients receiving either chemotherapy or radiation therapy. These studies were selected because they all used various forms of the Profile of Mood States fatigue and vigor subscales (17, 18), which facilitates comparisons and avoids the measurement problem encountered when using nonequivalent instruments. This instrument was selected because it is not based on activity or value systems but is a relatively pure measure of the sensation of CRF. The vigor subscale captures feelings of energy or pep and allows comparisons between fatigue and vigor. This issue is especially important as some studies include measures of energy rather than fatigue (19, 20) and the relationship between these concepts has not been examined in patients undergoing cancer treatment.

Instrument

The Profile of Mood States fatigue and vigor subscales are well established subscales with demonstrated internal consistency reliability (Cronbach's coefficient alpha = 0.94 and 0.89, respectively) and construct validity (17, 18). Each item is scored on a 0 = no fatigue to 4 = extreme fatigue; scores are summated. The number of items used in each version of the subscales varies by study; studies 1 and 5 used the 7-item fatigue and 8-item vigor subscales, studies 3 and 4 used the short form containing 5 fatigue and 5 vigor items, and study 2 used 6 fatigue and vigor items.

Although the POMS was originally developed as a measure of mood, it has been used widely as a measure of CRF. Some authors have used the POMS as a measure of mood, but eliminated the fatigue and energy subscales because the authors viewed the subscales as measuring treatment related side effects and not mood (19). The validity of the POMS as a measure CRF was determined in a multi-site instrumentation study, with strong correlations ($p < .001$) observed with five other measures of fatigue (20).

Statistical Procedures

Descriptive analyses were used to describe each sample and the patterns of CRF over time in each of the studies. Repeated measures analysis of variance (ANOVA) was used to determine differences over time in each of the studies. Study 5 used analysis of variance with post hoc tests to examine differences in fatigue and vigor by type of chemotherapy (doxorubicin and cyclophosphamide versus cyclophosphamide, methotrexate, and fluorouracil) and stage of disease. To maintain uniformity across samples, all analyses were performed in a consistent manner. Sample demographics for each of the studies are shown in table 1.

Results

Study 1 was designed to describe the process of coping with intracavitary radiation for gynecologic cancer (23). Intracavitary radiotherapy (ICRT) is a well-established treatment for various forms of gynecologic cancer. The rationale for the use of internal ICRT is that it allows a high dose of radiation to be delivered to the tumor while limiting the dose to adjacent tissues (24). The treatment technique used with subjects in this study required hospitalization and bedrest for the duration of the implant which was determined by the desired dose and strength of the radiation source. When intrauterine applicators are used, the applicator is placed under general anesthesia so the hospital stay also included all standard operative care procedures. Twenty-five women scheduled for treatment with an intrauterine (64%) or intravaginal (36%) radiation applicator were recruited from three radiation oncology practices in the northeastern USA. Subjects who agreed to participate gave written consent and were interviewed the evening before treatment (time 1), during treatment (time 2), the day after treatment (time 3), and 1-2 weeks following treatment (time 4). Each interview included the original 65-item version of the Profile of Mood States (17). The 7-item fatigue (scores range from a minimum= 0 to maximum=28) and 8-item vigor (scores range from a minimum= 0 to maximum=32) subscales were used in this analysis. The average duration of the treatment was 48 hours ($SD = 13.7$) with a minimum of 24 and a maximum of 75 hours.

CRF increased over the course of treatment (figure 1) with the greatest fatigue observed one day after treatment ended ($M=9.7$, $SD=8.7$). CRF declined in the 2 weeks following treatment and was only slightly elevated above pretreatment levels ($M=6$, $SD=6.9$). Vigor declined once ICRT began from a pretreatment mean of 17.5 ($SD=7.11$)

to a mean low of 13.1 (SD=9.6) during treatment. Vigor remained depressed in the 24-hours after ICRT ended (M=13.3, SD=6.8) but 1-2 weeks later rose to pretreatment levels (M = 17.6, SD=7.3).

The changes observed in CRF were not significant on repeated measures ANOVA ($F=3.91$, $p=0.059$, $df=3,72$). Repeated measures ANOVA demonstrated significant differences over time in vigor scores ($F = 5.05$, $p<.01$, $df 3, 72$). Differences in vigor were noted between pretreatment (time 1) and 1-2 weeks following ICRT (time 4), and between the during treatment (time 2) and 1-day after treatment (time 3) points. The small sample limits generalizability but provides valuable clinical information on a seldom-studied group of patients.

Study 2 was conducted to test the effects of two different approaches to supporting self-care in people beginning a course of cancer chemotherapy. Subjects (N=185) were recruited from the outpatient facilities of a university clinical cancer center and a university-affiliated community hospital. The sample was diverse with respect to type and stage of disease, and chemotherapy regimen. After written consent was obtained, subjects were randomized to one of three groups: a professional advice focused self-care instruction group; an experientially-focused self-care coaching group; or a usual care comparison group. Self-administered questionnaires, including a short form of the Profile of Mood States with a 6-item fatigue and 6-item vigor subscales (possible range of scores for each subscale = 0 to 24) were completed by subjects two and five days following the first two chemotherapy treatments. Questionnaires were returned to the study site by mail. Because the manipulated self-care variable did not produce any

significant group differences in CRF and vigor, data presented here are for the entire sample.

The mean Profile of Mood States fatigue scores showed a similar pattern over both cycles of chemotherapy (Figure 2). CRF was highest 2 days after treatment (cycle 1 $M=7.8$, $SD=5.0$; cycle 2 $M=7.6$, $SD=4.9$) with partial resolution observed 5 days after chemotherapy (cycle 1 $M=6.1$, $SD=4.6$; cycle 2 $M=6$, $SD=4.7$). Vigor scores were lowest 2 days after chemotherapy (cycle 1 $M = 5.5$ $SD = 4.4$; cycle 2 $M = 6.0$, $SD = 5.0$), with slight increases in vigor noted 5 days after chemotherapy (cycle 1 $M = 6.9$, $SD = 4.9$; cycle 2 $M = 7.2$, $SD = 4.8$).

There was a significant difference in CRF across time ($F = 13.9$, $p<.000$, $df\ 3$, 552). In both chemotherapy cycles, CRF scores on days 2 (time 1 and 3) and 5 (time 2 and 4) differed within each chemotherapy cycle ($p<.000$). However, neither peak (time 1 and 3) nor trough (time 2 and 4) levels significantly varied between the two treatment cycles. Significant differences in vigor scores across time were noted ($F = 12.8$, $p<.000$, $df = 3$, 549) with an opposite pattern of differences in vigor scores observed within both cycles of chemotherapy ($p<.000$).

Study 3 was the radiation treatment sample of a CRF instrumentation study. Subjects in this study ($N=92$) were recruited from four radiation treatment facilities located in the intermountain west and the East coast of the USA. This study reports only the data of completed cases ($N=63$) for the repeated measures analysis of variance. Subjects receiving external beam radiation treatment were recruited during the last week of treatment, a point when they were expected to experience high levels of fatigue. After giving written consent, subjects were oriented to an instrument packet that included the

brief Profile of Mood States (5-item fatigue and 5-item vigor subscales, with scores ranging from 0 to 20) and instructed to complete the instruments on the last week of treatment (time 1) and again four weeks later (time 2). Because multiple measures of fatigue were included in the study, subjects were randomly assigned to order of presentation of the instruments to avoid systematic carryover effects.

Results from this study indicate that CRF at the end of radiation therapy, a time when it is expected to be the highest (Figure 3), reached a mean high of 9.13 (SD = 6.1). Four weeks after radiation therapy had ended CRF scores had declined to a mean of 7.61 (SD = 5.4). Vigor scores were lower at the end of treatment (M = 6.14, SD = 5.0) than 4 weeks later (M = 8.01, SD = 5.4) when vigor scores began to show recovery. Significant differences were observed between the end of treatment and four weeks later for both CRF ($F = 8.9$, $p < .01$, $df 1, 62$) and vigor ($F = 13.9$, $p < .000$, $df 1, 62$).

Study 4 was the chemotherapy sample included in the fatigue instrumentation research described under study 3. Subjects (N=116) were recruited from five facilities in the intermountain West and East coast of the USA during a routine treatment visit. After giving written consent, subjects were oriented to the instrumentation packet and instructed to complete it two days after chemotherapy (time 1) and again the day before the next scheduled treatment (time 2). Repeated measures analysis of variance results are reported on 78 complete cases.

These results (Figure 4) clearly demonstrate a peak in CRF two days after chemotherapy (M = 9.18, SD = 6.0) and a decline in CRF before the subsequent treatment (M = 7.18, SD = 5.3). Vigor scores demonstrated the same pattern, but in the opposite direction. Vigor scores increased from a low 2 days following chemotherapy (M = 6.2,

SD= 5.1) to a mean of 8.4 (SD = 4.6) before the subsequent cycle of chemotherapy.

Significant declines in CRF were observed from 2 days after treatment to the time before the next treatment ($F = 7.0, p=.01, df 1, 77$). Significant increases in vigor scores were observed between the two measurement times ($F = 15.6, p<.000, df 1, 74$).

Study 5 was a study of women with breast cancer receiving adjuvant chemotherapy. The pattern of CRF during the first 3 cycles (each cycle was 3 weeks in length) of chemotherapy was examined in 61 newly diagnosed women with breast cancer. All stages of disease were represented, the majority of subjects had stage II infiltrating intraductal breast cancer and were receiving doxorubicin and cyclophosphamide (Table 2). After informed consent was obtained, all subjects completed baseline measures on the Profile of Mood States 7-item fatigue and 8-item vigor subscales (scores range from 0-28 and 0-32, respectively) and provided demographic information. Subjects were then contacted weekly, for 9 weeks, to re-administer the subscales.

Results show marked increases in CRF the week following each chemotherapy cycle (weeks 1, 4, 7), with the intensity of CRF increasing with each cycle of chemotherapy (Table 3). CRF gradually decreased between cycles, but never returned to baseline values (Figure 5). Vigor demonstrated the opposite pattern with scores decreasing in the week after each cycle of chemotherapy. Vigor improved after each cycle of chemotherapy, but never recovered to baseline levels.

Repeated measures ANOVA demonstrated significant differences in CRF across time ($F = 3.8, p<.000, df 9, 279$). Significant differences in decreasing CRF were observed from week 1 and week 2 within each cycle ($p<.05$), and increasing CRF from before treatment to after treatment in each cycle ($p<.01$). No differences in CRF were

noted by type of chemotherapy (doxorubicine and, cyclophosphomide [AC] or cyclophosphamide, methotrexate, flurouracil [CMF]) or stage of disease. Significant differences in vigor were observed across time ($F=3.12$, $p=.001$, $df\ 9, 315$) with declines in vigor noted between the beginning of cycle 1 (week 1) and 3 (week 7) ($p=.005$), and the end of cycle 1 (week 3) and beginning of cycle 2 (week 4) ($p=.03$). Although increases in vigor were observed in the second and third week of each treatment cycle, significant increases were noted between the beginning of cycle 3 (week 7) and the last week of that cycle (week 9) ($p=.001$). Differences in vigor were observed by type of treatment in the first week after each chemotherapy cycle (week 1, 4, and 7), with patients receiving CMF experiencing more vigor than subjects who received AC during weeks 1, 3, and 7 ($p<.05$). No differences in vigor were noted by stage of disease.

All subjects in this study experienced significant increases in CRF and declines in vigor within each chemotherapy cycle and across time. The differences in vigor noted between subjects receiving CMF and AC correspond to the week following chemotherapy. This finding suggests that the side effects of AC may be more severe and prolonged than those of CMF. Although the feelings of CRF may not differ by type of chemotherapy, subjects receiving CMF experienced more vigor and less CRF across all time points.

Relationship between CRF and Vigor

Within each study the correlation between fatigue and vigor scores at each point in time was computed, except for study 5 where the baseline and week of treatment points were selected for analysis (Table 1). There was a consistently strong, negative relationship between scores on the two subscales with the most variation exhibited in study 1 (minimum $-.406$ to maximum $-.745$), which had the smallest sample. Twelve of the

16 correlation coefficients fell between $-.560$ and $-.690$ indicating that fatigue and vigor consistently overlap 31% to 48%. When results are considered along with the pattern of change over time, it is clear that fatigue and vigor are related concepts, but that they should not be viewed as opposite ends of a continuum.

Conclusions

Each of these studies demonstrates a pattern of CRF that is specific to chemotherapy and radiation therapy. The CRF associated with chemotherapy peaks two to five days after treatment and remains elevated the week following each cycle of chemotherapy (study 2, 4 and 5). Chemotherapy-related CRF was observed to gradually resolve over time but never reached pretreatment values. Subjects in study 4 were observed to have markedly higher CRF than subjects in the other chemotherapy studies. The reason for this finding is unclear.

In study 5, CRF in women with breast cancer increased with each cycle of chemotherapy to increasingly higher peak levels. This stair-step pattern reflects the increasing intensity of CRF over the course of multiple treatment cycles. In contrast, the pattern of CRF, in study 2, was slightly higher during the first cycle of chemotherapy than the second cycle. The changes from cycle 1 to cycle 2 were so small in this study that it is difficult to assess the cause of the changes, which are made even more difficult to evaluate because of the diversity of types of disease and treatments. Possibly these patients developed a schema of what to expect from the CRF that in turn helped them cope with the CRF experienced during the second cycle of chemotherapy. An alternative explanation is that the manipulated self-care variable may have had a statistically

nonsignificant but clinically significant effect on CRF. However, increases in CRF before subsequent cycles of chemotherapy have been observed in another study (5), suggesting a possible anticipatory or psychological effect.

Subjects in study 4 showed modest declines in CRF from very high levels two days after chemotherapy to slightly lower levels before the subsequent treatment cycle. These subjects were not studied over time, and represent a diversity of types and stages of cancer and types of treatment which make interpretation of the results complex. However, the small declines in CRF from time 1 to time 2 suggests the stair-step pattern and chronicity of the symptom. A different pattern has been observed in patients receiving continuous versus bolus chemotherapy, with patients receiving continuous infusions having more prolonged peak CRF (5).

CRF has been hypothesized to increase during the hematologic nadir and decrease before the next cycle of therapy (25). This finding was not demonstrated in study 5 which measured CRF weekly over three chemotherapy cycles. In a sample of 31 women with breast cancer, daily measures of CRF failed to demonstrate a rise in CRF during the nadir (26). The lack of a nadir effect observed in this sample may demonstrate differences in the intensity of therapies for different stages and types of disease and treatment, as these findings can only be generalized to women with breast cancer.

Radiation therapy related fatigue shows a pattern of gradual accumulation over time. The spike in CRF after treatment ended was similar in patients receiving ICRT and patients receiving chemotherapy. However, ICRT patients' CRF returned to near baseline values within 5 days after completing treatment. The quick resolution of CRF that was observed in this small sample is in contrast to the slow declines in CRF observed in

patients after external beam radiation therapy when a single item measure was used (27).

Study 3 demonstrates the prolonged presence of CRF after external radiation therapy ends. Patients report that CRF is the most difficult side effect of radiation therapy to cope with because recovery to pretreatment levels is so prolonged (27). The very slow return to baseline CRF levels may reflect an actual, but not understood, physiologic response to therapy, or a gradual psychosocial re-adaptation to a regular work and life schedule. The physiologic explanation is more plausible given the incidence and severity of the symptom. However, our lack of understanding of the mechanism of CRF makes either explanation reasonable.

As expected, the pattern of vigor is in a different direction from CRF. When CRF scores peak after chemotherapy or radiation therapy, vigor scores tend to decline. As recovery from either chemotherapy or radiation therapy begins and CRF declines, vigor scores begin to rise. While vigor and CRF move in opposite directions they do not completely mirror each other with respect to degree of change in either direction. These two patterns demonstrate the complex and multidimensional nature of CRF.

A significant limitation of all of these studies is that none controlled for the effects of response-shift bias. This form of bias may have resulted in patients underreporting their CRF once they had experience with the sensation and reset their standard of comparison (28). The response shift phenomenon may account for the declines in peak CRF from cycle 1 to cycle 2 observed in study 2. A weakness of studies 2, 3, and 4 is that subjects were diverse with respect to type of treatment and stage of cancer. While this was optimal for the original intent of the instrumentation studies, it poses limitations for interpretation

except to note the pervasive nature of CRF across all types of cancer, stages of disease and types of treatment.

As more is understood about the nature of CRF, interventions will become more focused on causal mechanisms. Although we are learning more about the patterns of CRF associated with different types of treatments, it is clear that biotherapy, radiotherapy, ICRT, and chemotherapy protocols have unique CRF patterns and that person-related variables, such as age and gender, influence CRF (5, 13, 29, 30).

As practitioners it is important to inform patients about the pattern of CRF that is commonly experienced by patients receiving chemotherapy or radiation therapy. Preparing patients for an unknown and often feared experience allows them to prepare for and understand what to expect. Keeping patients educated and informed opens communication between patient and provider and reduces patient anxieties about treatments and treatment related complications.

References

1. Richardson A: Fatigue in cancer patients: a review of the literature. *Eu J Cancer Care* 4:20-32, 1995.
2. Glaus A, Crow R, Hammond S: A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals: supportive care. *Supportive Care in Cancer* 4:82-96: 1996.
3. Piper B, Lindsey, A, Dodd M, et al: The development of an instrument to measure the subjective dimension of fatigue. In: *Key Aspects of Comfort: management of pain, fatigue, and nausea*, edited by S Funk, et al, New York, Springer, 1989, pp 199-208.
4. Meyerowitz B, Spark F, Spears I: Adjuvant chemotherapy for breast carcinoma: psychosocial implications. *Cancer* 43:1613-18, 1979.
5. Richardson A, Ream E, Wilson-Barnett J: Fatigue in patients receiving chemotherapy: patterns of change. *Cancer Nurs* 21:17-30, 1998.
6. Nail L, Jones L, Greene D, et al: Use and perceived efficacy of self-care activities in patients receiving chemotherapy. *Oncol Nurs Forum* 18:883-7, 1991.
7. Nail LM, King K: Fatigue: a side effect of cancer treatments. *Sem Oncol Nurs* 3:257-62, 1987.
8. Nail LM, Winningham ML: Fatigue and Weakness in cancer patients: The symptom experience. *Sem Oncol Nurs* 11: 272-78, 1995.
9. Schwartz A: Patterns of exercise and fatigue in physically active cancer survivors. *Oncol Nurs Forum* in press.
10. Fobair P, Hoppe R, Bloom L: Psychosocial problems among survivors of Hodgkin's disease. *J Clin Oncol* 4:805-814, 1986.
11. Pickard-Holley S: fatigue in cancer patients: a descriptive study. *Cancer Nurs* 14:13-19, 1991.
12. Stephen SA, Nail LM: Age-related differences in perceived fatigue in persons receiving treatment for cancer. Poster presentation, Western Institute of Nursing, Portland, OR, May 1-3.
13. Pater J, Zee B, Palmer M et al: Fatigue in patients with cancer: results with National Cancer institute of Cancer Clinical trials Group studies employing the EORTC QLQ-C30. *Support Care Cancer* 5:410-13, 1997.
14. Nerenz DR., Leventhal H, & Love RR.: Factors contributing to emotional distress during cancer chemotherapy. *Cancer*, 50:1020-1027, 1982.
15. Pater JL, Loeb M: Nonanatomic prognostic factors in carcinoma of the lung. A multivariate analysis. *Cancer* 50:331-336, 1982.
16. Weeks J: Quality-of-life assessment: performance status upstaged? *J. Clin Oncol* 10:1827-29, 1992.
17. McNair DM, Lorr M, Droppleman LF: Profile of mood states manual. San Diego: Educational and Industrial Testing Service, 1971.
18. McNair DM, Lorr M, Droppleman L F: Profile of mood states manual. San Diego: Educational and Industrial Testing Service, 2nd edition, 1992.
- 19 Johnson, JE, Nail, LM, et al. (1988). Reducing the negative impact of radiation therapy on functional status. *Cancer* 61:46-51, 1988.

20. Nail, LM, Meek, PM, et al. Evaluating the properties of brief fatigue instrument for use with cancer patients. Paper presented at the Advanced Research SIG meeting, Oncology Nursing Society Congress, New Orleans, LA, 1997.
21. Glaspy JA, Economic outcomes associated with the use of hematopoietic growth factors. *Oncology (Huntington)* 9:93-105, 1995.
22. Glaspy J, Bukowski R, Steinberg D. Impact of therapy with epoetin alfa on clinical outcomes in patents with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. *J Clin Oncol* 15:1218-1234, 1997.
23. Nail LM: Coping with intracavitary radiation therapy for gynecologic cancer. *Ca Prac*. 1:218-224, 1993.
24. Fleming ID, Brady LW, Glenn B et al. Basis for major current therapies for cancer. In: American Cancer Society textbook of clinical oncology, edited by G. Murphy, W. Lawrence, RE Lenhard, New York, American Cancer Society 2nd edition, pp. 107-110.
25. Winningham ML, Nail LM, Burke MB, et al: Fatigue and the cancer experience: The state of the knowledge. *Oncol Nurs Forum* 21:23-36, 1994.
26. Schwartz AL: The relationship of exercise to fatigue and quality of life in women with breast cancer. Unpublished dissertation, University of Utah, 1997.
27. Walker BJ, Nail LM, Larsen L: Experiences following the completion of radiation treatment. *Oncol Nurs Forum* 23:1181-87, 1996.
28. Breetvelt IS, Van Dam FSAM: Underreporting by cancer patients: The case of response-shift. *Soc Sci Med* 32: 981-987, 1991.
29. Sitzia J, North C, Stanley J et al: side effects of CHOP in the treatment of non-Hodgkin's lymphoma. *Cancer Nurs* 20:430-439, 1997.
30. Sitzia J, Huggins L: Side effects of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy for breast cancer. *Ca Prac* 6:13-21, 1998.

Table 1. Demographic data for the 5 studies and correlations of fatigue and vigor.

Variable	Study 1	Study 2	Study 3	Study 4	Study 5
N of subjects	25	185	92	116	61
Treatment	ICRT	CTX	RT	CTX	CTX
Diagnosis (%)					
Gynecologic	100		4	7	
Breast (Female)		44	31	37	100
Lung		7	8	6	
Colorectal		16			
HL/NHL		14	3	17	
Bladder/urethra		4			
GI		2	11	15	
Leukemia				5	
Head & Neck			8		
Prostate			26	3	
CNS		2			
Other		11	9	11	
Mean age in years (SD)	58.4 (15.1)	54.6 (13.6)	59.9 (12.2)	53.8 (14.2)	47.1 (7.9)
Minimum age	31	18	19	19	27
Maximum age	90	82	86	78	69
% Female	100	69	51	62	100
Highest Education					
< HS graduate	43	12	16	9	
HS graduate	36	32	29	30	18
> HS	21	56	55	61	82
Race (%)					
White	100	90	92	97	90
African-American		9	2	1	
Hispanic			2		2
Other		1	4	2	8
Employment Status (%)					
Retired	36		38	29	5
Employed FT	35		36	27	49
Employed PT	4		13	9	15
Homemakers	21		11	13	26
Not working	4		2	22	5
Marital Status (%)					
Single	7	9	4	7	5
Married	43	72	81	77	72
Widowed	29	11	7	6	5
Divorced/Separated	21	8	8	10	18
Correlation CRF & Vigor*					
Time 1	-.745**	-.605**	-.689**	-.637**	-.563**
Time 2	-.586**	-.615**	-.676**	-.640**	-.605**
Time 3	-.612**	-.651**			-.590**
Time 4	-.400*	-.590**			-.507**

HS = high school; FT = full time; PT = part time

* $p < .05$ ** $p < .01$

Time 1-4 Study 5 = baseline, weeks 1, 4, and 7

Table 2. Stage of disease and type of treatment of subjects in study 5.

	N	%
Stage of Disease		
I	10	16.4
II	33	54.1
III	12	19.7
IV	6	9.8
Type of Treatment		
CMF ^a	23	37.7
AC ^b	37	60.7
Navelbine	1	1.6

a= cyclophosphamide, methotrexate, flurouracil

b=doxorubicine, cyclophosphomide

Table 3. Fatigue and Vigor scores over 9 weeks of chemotherapy (study 5).

	Mean	SD
Fatigue		
Baseline	7.11	6.12
Week 1*	10.28	6.77
Week 2	7.50	6.91
Week 3	8.68	6.50
Week 4*	10.25	7.15
Week 5	8.14	6.07
Week 6	8.04	5.78
Week 7*	11.49	7.62
Week 8	8.82	7.07
Week 9	7.94	6.46
Vigor		
Baseline	14.77	6.83
Week 1*	13.89	7.11
Week 2	14.73	6.67
Week 3	14.25	7.43
Week 4*	12.36	7.84
Week 5	13.65	6.89
Week 6	12.16	6.47
Week 7*	10.54	6.51
Week 8	12.97	8.32
Week 9	14.25	7.51

- = chemotherapy weeks

Figure 1. Mean POMS fatigue and vigor scores in women receiving ICRT (study 1).

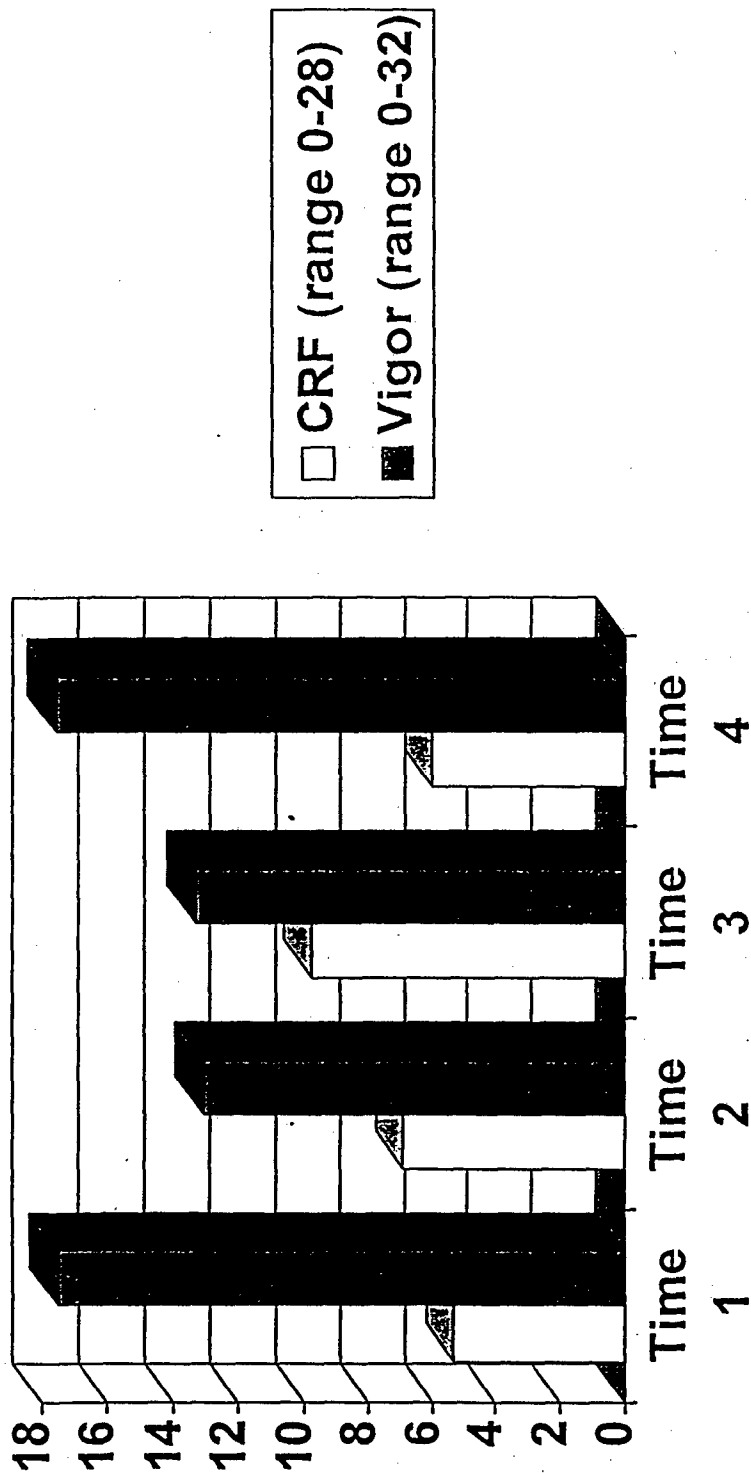


Figure 2. Mean POMS fatigue and vigor over 2 cycles of chemotherapy (study 2).

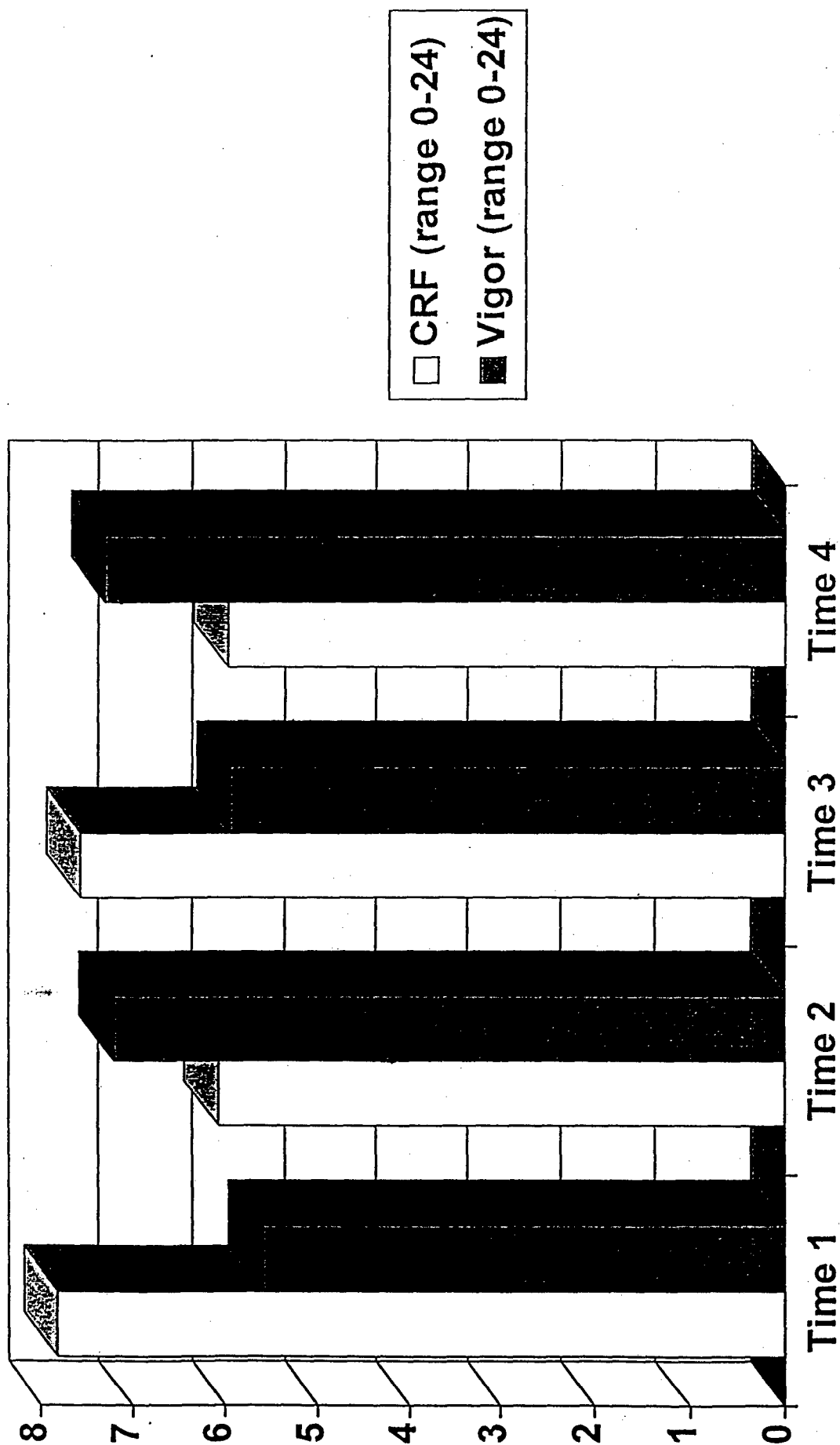


Figure 3. Mean POMS CRF and vigor scores from end of radiotherapy (Time 1) to 28-days later (Time 2) (study 3).

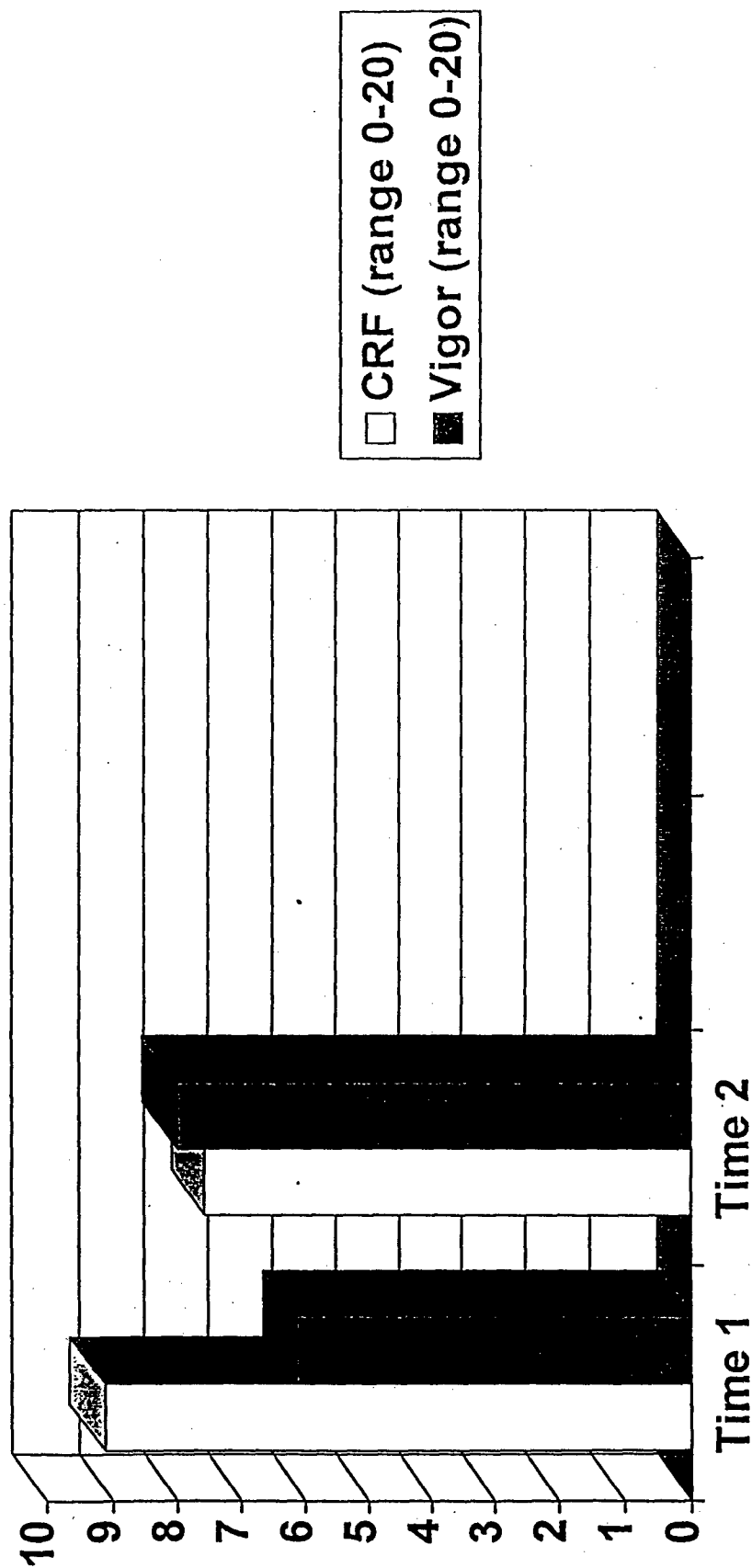


Figure 4. Mean POMS fatigue and vigor scores from end of a chemotherapy cycle (Time 1) to 24 hours before next treatment (Time 2) later (study 4).

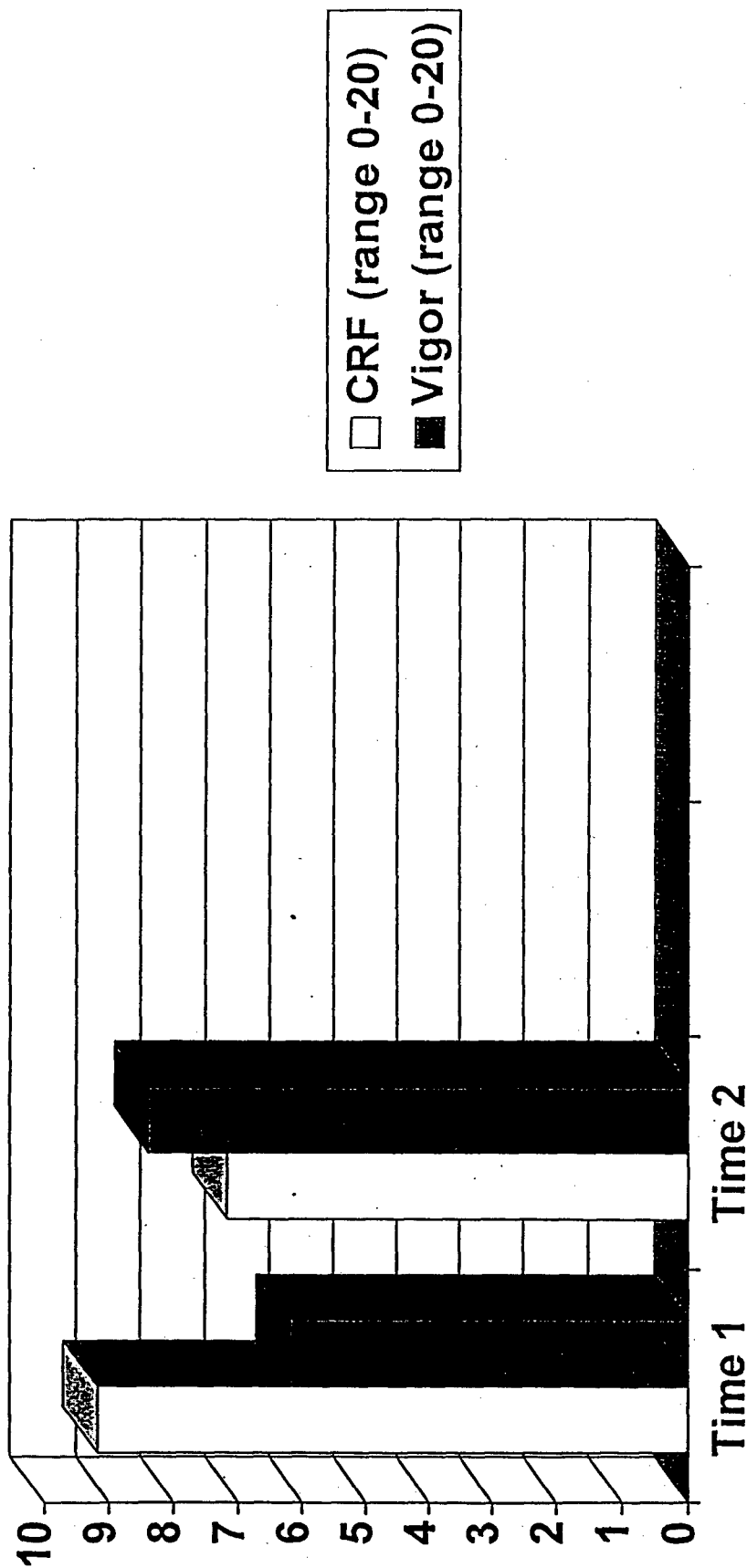
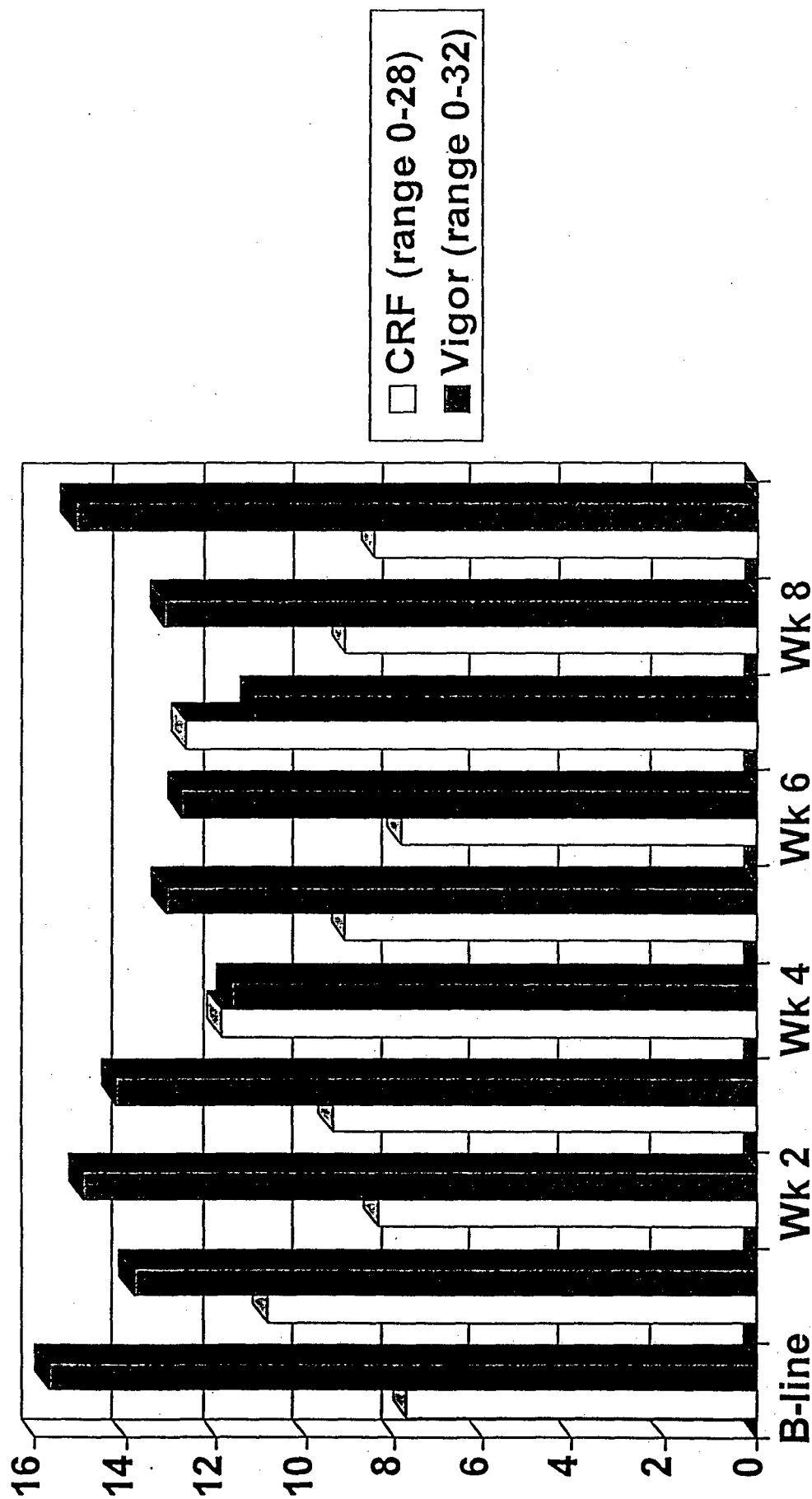


Figure 5. Mean weekly POMS fatigue and vigor scores over 3 cycles of chemotherapy (study 5).



Exercise and fatigue: Day-to-day variation.
In Review, *Nursing Research*.

Privileged Communication

Exercise and Fatigue:

Day to Day Variation in Women with Breast Cancer Receiving Chemotherapy.

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Running Head: Exercise Dose and Fatigue

Abstract

Background/Objectives: Cancer treatment-related fatigue (fatigue) is the most prevalent and distressing symptom of cancer therapy. Interventions to minimize fatigue are needed. The purpose was to examine the relationship between exercise and fatigue over the first three cycles of chemotherapy in women receiving cyclophosphamide, methotrexate and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) for breast cancer.

Methods: Seventy-two newly diagnosed women with breast cancer were instructed in an 8-week home-based low-intensity exercise intervention. Measures of functional ability, energy expenditure, fatigue and side effect severity were obtained at baseline and posttest. Subjects maintained daily records of 4 types of fatigue, and exercise duration, intensity and type.

Results: Exercise demonstrated a strong effect on reducing fatigue intensity. A sublinear relationship between fatigue and duration of exercise indicated that as the number of minutes of exercise increased fatigue declined. Baseline fatigue was not associated with number of days of exercise or amount of exercise, suggesting that fatigue level does not predict exercise. Side effect severity was negatively associated with both exercise frequency and duration.

Conclusions: The impact of exercise on fatigue was strong and suggests the effectiveness of a low-to-moderate intensity regular exercise program in maintaining functional ability and reducing fatigue in women with breast cancer undergoing chemotherapy. This study supports further investigation of the effects of exercise on fatigue in a randomized trial.

Background

Everyday people experience fatigue. Fatigue is a symptom commonly associated with diseases such as depression, multiple sclerosis, arthritis and renal disease, and different medical and pharmacological treatments. Persons being treated for cancer experience a different and far more disruptive form of fatigue. Cancer treatment-related fatigue (fatigue) is the most prevalent and disturbing side effect of treatment for the majority of cancer patients (Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Irvine, Vincent, Graydon, & Bubela, 1998; Richardson, Ream, Wilson-Barnett, 1998). Fatigue leads to declines in emotional, psychosocial and physical function (Dimeo et al, 1997; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Mac Vicar, & Winningham, 1986; Mock et al, 1997; Mock et al 1994; Winningham et al, 1994; Young-McCaughan & Sexton, 1991). Fatigue is described as being relentless and intense; a type of fatigue that is more severe, unpredictable and overwhelming than the fatigue experienced before cancer treatment (Nail & Winningham 1995; Schwartz 1998). The symptom is often misinterpreted by the patient as advancing disease or failure to respond to treatment. Fatigue peaks 2-3 days after receiving bolus chemotherapy and reports conflict whether fatigue increases again during the nadir (Richardson, Ream, & Wilson-Barnett, 1998; Schwartz, 1997, in press). Fatigue continues to affect patients years after treatment has ended making fatigue an ongoing issue for long term survivors (Fobair, Hoppe, & Bloom, 1986; Schwartz, 1998).

A complex, multifactorial phenomenon, fatigue is difficult to define. It is a self-perceived, subjective experience that is unpredictable, not completely resolved with rest,

and negatively interferes with quality of life (Winningham 1994; Piper, 1993; Irvine 1998). Despite the importance of fatigue, the mechanisms underlying it are not understood, and little is known about managing it. The positive effects of exercise in prevention of disease and promotion of health are noteworthy, and address the quality of life domains relevant to fatigue (Patt et al, 1995). Studies with cancer patients have demonstrated positive effects of exercise on mood, chemotherapy side effect severity, weight gain, functional ability and quality of life (Dimeo et al, 1997; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger & Keul, 1998; Mac Vicar, & Winningham, 1986; Mock et al, 1997; Mock et al 1994; Schwartz, 1997, 1998; Winningham et al, 1994; Young-McCaughan & Sexton, 1991). In the only study which examined how exercise improves quality of life in women with breast cancer (Schwartz, 1997), fatigue mediated the effect of exercise on quality of life.

In previous studies, the conclusion that exercise decreases fatigue was based on a single composite score which aggregated data over several days or weeks (Dimeo et al, 1997; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Mock et al, 1997; Mock et al 1994), or the method of measuring fatigue was not described (Dimeo, Rumberger & Keul, 1998). However, there is a dramatic day-to-day fluctuation in fatigue, which is not addressed or captured using the aggregated approach. Understanding the relationship between exercise and fatigue within relatively brief time frames is essential in determining what dose of exercise should be prescribed and in determining the shape of the dose-response relationship.

The purpose of this analysis was to examine the relationship between exercise and fatigue over the first three cycles of chemotherapy in women receiving either

cyclophosphamide, methotrexate and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) for stage I to III ductal carcinoma of the breast. The six research questions we examined were: (1) Does exercise decrease level of fatigue on the same day? (2) Does the amount of exercise correlate with fatigue level? (3) Is there a curvilinear effect of exercise on fatigue level? (4) Is there a cumulative effect of exercise on fatigue? (5) Is the effect of exercise transient or long lasting? (6) Is there a relationship between exercise intensity and fatigue level?

Method

A one-group pretest-posttest design was used to examine the relationship between fatigue and exercise in women with breast cancer who participated in an 8-week home-based exercise intervention.

Sample. Seventy-two women enrolled in the study. Results are presented on the 61 subjects who completed the study and maintained exercise and fatigue diaries. The 12 subjects who did not complete the study either did not complete the fatigue measures (N=5), were lost to follow-up (N=1), or withdrew from the study (N=6). No differences in demographic characteristics ($\chi^2 > .05$) were observed between those who completed the study and those who did not. Subjects ranged in age from 27 to 69 years old (M= 47.3 years old, SD=7.9). The majority of subjects were married (72.1%), employed (64%), Caucasian (90.2%), and had attended some college (78.7%). Most participants were being treated on a 21-day cycle of AC (60.7%) for stage II (54.1%) infiltrating ductal carcinoma of the breast. All subjects had surgery at least 21 days before beginning the study, with 73.8% having partial mastectomy with nodal dissection. None of the subjects had received radiation therapy prior to study entry. Fifty-eight percent of the sample did

not exercise at entry into the study. The subjects who were regular exercisers at baseline (42%) reported exercising an average of 38 minutes, 4 days per week. Walking was the primary exercise for these women.

Procedures. Potential subjects were recruited to participate in an eight-week home-based aerobic exercise program, from a university cancer center and private practice. All eligible subjects (chemotherapy naive, no previous radiotherapy, ambulatory with histologically documented breast cancer) were invited to participate in the study. After informed consent was obtained, all baseline measures were obtained before the first cycle of chemotherapy. These measures included: 12-minute walking distance, Caltrac™ accelerometry, daily visual analogue measures of fatigue, and Side Effect Symptom Checklist.

All women received verbal and written instruction to exercise between 15 to 30 minutes, 3 to 4 days a week and to wear the Caltrac with each exercise session. Women were instructed to exercise at an intensity that did not aggravate their symptoms (e.g. pain, fatigue). To improve adherence to exercise and because the benefits of aerobic exercise are not determined by type of activity as much as by exercise intensity and duration, the women were encouraged to choose an aerobic activity they enjoyed. All of the women received information about contraindications to exercise and were given a 24-hour contact number to call if they had questions regarding their exercise program or how to operate their Caltrac. Weekly telephone calls, conducted by a research assistant, were used to remind subjects to return their exercise and fatigue diaries and administer the weekly measure of side effects.

Measures. Demographics. Demographic variables recorded included age, ethnicity, marital status, education, and previous exercise behavior. Chart review was used to obtain clinical information such as stage of disease and chemotherapy regimen.

Functional ability. The 12-minute walk is a measure of the distance in feet an individual can cover in 12-minutes. Baseline and posttest measures were used to assess changes in functional ability resulting from exercise. All subjects followed a measured course, received consistent instructions and were encouraged only in the last 2 minutes of the walk. The tests were conducted indoors in a climate-controlled environment. The 12-minute walk is strongly correlated ($r=0.9$) with oxygen consumption (Cooper, 1963), and has been successfully used in studies with women with breast cancer (Mock et al, 1994; 1997; Schwartz, 1997) and is used extensively in cardiopulmonary rehabilitation as a measure of functional ability (Bernstein et al, 1994; Steele, 1996; ZuWallack, Patel, Reardon, Clark, & Normandin, 1991). The 12-minute walking distance is relevant to daily activities and the test is easily administered in a clinical setting.

Exercise intensity. Caltrac™ accelerometers (Muscle Dynamics Fitness Network, Torrence, CA) were used to record the amount of energy (calories) expended, or exercise intensity, during the 12-minute walks and in each exercise session. The Caltrac has demonstrated test-retest reliability, interinstrument reliability, and strong correlations with maximum oxygen uptake and doubly labeled water (Brokoski, Pivarnik, & Morrow, 1991; Montoye, Washburn, Seavers, Eritt, Webster, & Nagle, 1983; Sallis, Buono, Roby, Carlson, & Nelson, 1990; Pambianco, Wing, & Robertson, 1990; Gretebeck & Montoye, 1992). Reliability and validity have been demonstrated for walking, running and cycling (Haymes & Byrnes, 1991; Hunter et al, 1989; Pambianco, Wing, & Robertson, 1990).

Subjects recorded calories expended during exercise, as measured by the Caltrac™, in an exercise log that included information about frequency, type and duration of exercise.

Self-reported measure. Fatigue diaries were used to record, on four 100-mm visual analogue scales (VAS-F), the level of (1) fatigue at its worst in the past 24 hours, (2) fatigue at its least in the past 24 hours, (3) fatigue on the average, and (4) fatigue right now. For consistency of measurement, subjects were instructed to complete the diary at the same time each night before they went to bed. This helped make recording fatigue part of their nightly routine. Subjects who recorded data for each day produced 56 measures each of worst, least, average and fatigue right now. Visual analogue scale has been successfully used in previous studies to measure cancer-related fatigue (Blesch, et al, 1991; Mock et al, 1994; Richardson, 1998; Schwartz, 1998a).

Analytic Techniques

Descriptive statistics were used to describe the sample and measures of functional ability. Only for the descriptive analysis of functional ability were the women categorized as exercisers or nonexercisers. This categorization was based on whether a woman improved or declined on the posttest 12-minute walk. The daily fatigue data were analyzed using unbalanced repeated measures analysis (Jennrich & Schuster, 1986) to examine the research questions. Although measures of fatigue were obtained daily for 8 weeks (56 days), we limited our analysis to the first 6 weeks (42 days) of treatment because of missing data; this included all of the women who completed the study (N=61). The presence or absence of exercise, number of minutes exercised, and cumulative amount of exercise were evaluated as time-dependent covariates in the analysis. This variance-

covariance matrix was assumed to have a toeplitz structure with seven bands. This implies that the fatigue measured within six days are correlated, while the fatigue measured more than six days are uncorrelated (e.g., the correlation between day 1 and day 7 is zero).

Given that fatigue is a highly variable state and not a trait characteristic, this assumption was appropriate. All analyses were performed using PROC MIXED procedures in the Statistical Analysis System, Version 6.12 (SAS Institute; 1996).

Results

Descriptive Analysis of Measures.

Sixty percent (N=36) of the women adopted the exercise program as demonstrated by improvements in functional ability. Subjects who did not maintain or improve their functional ability on the 12-minute walk and recorded exercise data in the exercise log were defined as non-exercisers. These women either did not adopt the exercise intervention or did not adhere sufficiently to obtain functional ability benefits. Although 60% adherence rate exceeds that generally observed in exercise studies, it is unclear why the other 40% of the sample did not adopt exercise. Many of these women were obese and were not previously exercisers, two factors that are the strongest predictors of who will adopt an exercise program (McAuley, Courney, Rudolph, & Lox, 1994).

The mean baseline 12-minute walking distance for the group was 3449 ft (SD=649, min/max=1923-4990). Subjects who adopted the exercise program (n=36) increased the posttest 12-minute walking distance (M=3914 ft, SD=624, min/max=2325-5747); demonstrating a mean increased functional ability at posttest of 15% (SD=14.1,

min/max=1-58%, $p<.000$). Subjects who did not adopt the exercise program ($n=24$) decreased the 12-minute walking distance at posttest ($M=2938$ ft, $SD=679$, min/max=1763-3934); declining a mean of 16% ($SD=13\%$ min/max=-2-48% $p<.000$). Nine subjects who were regular exercisers at baseline did not continue to exercise during the study period. While one of the subject's functional ability declined 37% ($M=22\%$, $SD=13\%$), 5 of the subjects showed only modest declines ($M=4\%$) in functional ability. These subjects may have been categorized as non-exercisers by virtue of the stringent criteria used to define those subjects who adopted the exercise program when they really maintained an exercise program but at a lower intensity, frequency or duration than prior to beginning chemotherapy. The 35 women who were nonexercisers at baseline, but adopted the exercise program demonstrated improvements in functional ability ($M=15.8\%$, $SD=16.4$, range=1%-58%) over the study period.

The daily VAS-F measures proved difficult to analyze because of the high degree of variability. Scores on all four of the daily fatigue measures ranged from 0 to 100, with extreme variability observed within each subject.

Research Questions:

Does exercise decrease level of fatigue on the same day?

A comparison of the four measures of fatigue on non-exercise and exercise days revealed a strong effect of exercise on fatigue (Table 1). All measures of fatigue were significantly reduced on the exercise days in comparison to the non-exercise days.

Because subjects recorded their fatigue at night, it can be assumed that the declines in fatigue on exercise days were related to exercise, and not simply that people exercised because they felt better or experienced fewer symptoms. Exercise effects appear to

remain constant over time as indicated by an insignificant interaction between exercise and time (all p values $>.3$). The effects of exercise remained significant even after adjusting for baseline level of fatigue and functional ability (all p values $<.0001$).

Does the amount of exercise correlate with the fatigue level?

The amount of exercise, measured as the number of minutes exercised, was significantly associated with fatigue levels (Table 2). In general, the longer a woman exercised, the less fatigue she felt on that day. The exception was for current level of fatigue (fatigue now) which increased when exercise exceeded 60 minutes. The reason for the increase in current level of fatigue is unclear. Prolonged exercise may provoke muscular fatigue and fatigue associated with changes in nutrition and hydration states that could increase the sensation of current level of fatigue.

Is there a curvilinear effect of exercise on the fatigue level?

Among those who exercised, the majority of patients exercised less than 2 hours. Therefore, we focused on characterizing the relationship between fatigue and minutes of exercise less than 2 hours. In order to find the best fitting model, we evaluated the following four models:

Model 1 (linear): $E(y_{ij}) = \beta_{0j} + \beta_1 x_{ij}$

Model 2 (logarithmic): $E(y_{ij}) = \beta_{0j} + \beta_1 \log(x_{ij}+0.5)$

Model 3 (reciprocal): $E(y_{ij}) = \beta_{0j} + \beta_1 \times 1/(x_{ij}+0.5)$

Model 4 (square root): $E(y_{ij}) = \beta_{0j} + \beta_1 x_{ij}^{1/2}$

$E(y_{ij})$ represents the expected fatigue level for the i th subject on the j th day, whereas x_{ij} represent the minutes of exercise. The parameter β_{0j} represents the expected fatigue level of the j th day in the absence of exercise (e.g. $x_{ij} = 0$). The above models were evaluated

using number of minutes of exercise as a continuous variable in the unbalanced repeated measures analysis.

There appears to be no strong curvilinear relationship between fatigue and minutes of exercise during the first 2 hours of exercise (Figure 1). The more one exercised, the less fatigue one felt. Furthermore, the relationship appears to be sub-linear. The best fitting model was Model 4, which describes the linear relationship between fatigue and the square root of the number of minutes exercised. The model predicts a steeper decline in fatigue in the first hour of exercise and a linear decline between 1-2 hours of exercise. The decline in fatigue is most acute in the first 15-20 minutes of exercise. Table 3 summarizes the estimated regression coefficients for four types of fatigue. Figure 1 illustrates the predicted fatigue levels as a function of the minutes of exercise. Although the declines in fatigue were consistently strong across the four types of fatigue, the decline in current level of fatigue was greatest. This may reflect the feeling of increased energy that patients report after exercise (Schwartz, 1998).

Is there a cumulative effect of exercise?

The analysis of cumulative amount of exercise, measured by cumulative days of exercise ($M=12.12$, $SD=11.43$, $\text{min/max}=0-42$) and cumulative minutes of exercise ($M=434.6333$, $SD=610.15$, $\text{min/max}=0-1878$), showed a weaker, inconsistent association with reduced fatigue levels. The effect of exercise on fatigue appears to be more immediate, and does not necessarily carry over to subsequent days. Table 4 summarizes the results of the analysis of cumulative minutes of exercise on the four measures of fatigue. The trend was for fatigue to decrease as the cumulative number of minutes of

exercise increased, but the results show a slight increase in the worst, average and current level of fatigue in persons who exercised a total of between 2 and 5 hours.

Is the effect of exercise transient or long-lasting?

In order to evaluate whether the effects of exercise persist from one day to the next, we categorized the data according to the presence or absence of exercise on the current or previous day (Table 5). Although there appears to be a small carry-over effect of exercise to the next day, the impact of exercise on fatigue appears to be more immediate. Fatigue was lowest when a woman exercised 2 days in a row; somewhat higher when she exercised one day but not the next day; and still higher when she did not exercise at all in the 2 day period (Table 6). These results show the immediate effect of exercise and a small but significant carry-over effect of exercise on fatigue.

Is there an association between the exercise intensity and the fatigue level?

Exercise intensity was measured by the number of calories expended during exercise as recorded by the Caltrac accelerometer. The effects of the calories expenditure on the level of fatigue are summarized in Table 7. In general, as caloric expenditure increased, fatigue declined. However, the effects of exercise intensity were only significant for the least fatigue ($p=.0402$) and the average fatigue ($p=.0359$). These results suggest that when a woman exercises at moderate to high intensity levels her perceptions of worst and current level of fatigue are not changed.

Discussion

Although this study is limited by the single group design, it provides evidence that women undergoing chemotherapy for breast cancer will follow a home-based exercise intervention and demonstrates the success of the intervention in promoting functional ability. The impact of exercise on fatigue was strong and reflects the effectiveness of low-intensity regular exercise in maintaining functional ability and reducing fatigue in patients with breast cancer. The magnitude of declines in fatigue on exercise days, and by type of fatigue was remarkable. Exercise reduced the intensity of fatigue between 14% and 35%, depending on type of fatigue. Although the effects of exercise on current level of fatigue were somewhat inconsistent and weaker than for the other types of fatigue, most subjects recorded their fatigue at night when one usually feels most tired. The presence of exercise consistently was associated with reducing fatigue the day of exercise and one day afterward.

Determining the optimal dose of exercise to reduce fatigue is elusive. The inconsistent findings related to the cumulative effects and duration of exercise on fatigue lead one to speculate that daily or every-other day exercise may be optimal to reduce fatigue. Brief periods of regular aerobic exercise for at least 10 to 25 minutes appear to confer the greatest declines in all types of fatigue (Figure 1). However, the steep decline in fatigue observed with short bouts of exercise suggests that even brief periods of exercise may be sufficient to reduce fatigue. Clearly exercising for longer duration reduces fatigue more, but providing an exercise recommendation that is realistic and achievable for women is paramount. Given the sedentary lifestyle of the majority of healthy persons, and the propensity for cancer patients to increase rest, the findings that minimal exercise

reduces fatigue are encouraging (Dimeo et al 1997; Dimeo, Fetscher, Lange, Kertelsmann & Keul, 1997). Breast cancer patients who begin an exercise program of regular, short bouts of low-to-moderate exercise and gradually increase duration as their fitness levels improve may reap the benefits of improved functional ability and markedly reduced fatigue.

In this study, subjects were instructed to exercise at an intensity that was symptom limited. Consequently, the majority of women who adopted the exercise program walked and engaged in other low-to-moderate intensity exercise. This exercise intensity was acceptable to the women, and produced favorable outcomes; a finding concurrent with epidemiologic studies that have demonstrated the benefits of low intensity, regular exercise in promoting health and reducing morbidity (Lorig, et al, 1999; Pate et al, 1995).

In this study, women could chose not to exercise without being admonished for not adhering to the exercise intervention. While all the women who enrolled in the study expressed an interest in exercise and intent to exercise, clearly not all subjects were able to comply with this very modest exercise prescription. Identifying characteristics of women who would benefit from a more structured supervised exercise programs will be important to promoting exercise for all women with breast cancer.

Limitations

The generalizability of the study is limited by the one-group design. The use of self-reported measures of exercise and fatigue, while an inherent weakness of the study, was logistically necessary. However, the strong correlation between duration and frequency of exercise suggests that subjects accurately reported exercise. An indirect benefit of the one-group design was that subjects were told that the exercise program they

were instructed to follow was a guide. This allowed subjects to exercise or not exercise without feeling they would be negatively judged, which may have prevented inflated self-reports of exercise and reduced subjects' feelings of guilt. Similar to previous exercise studies, the sample is predominantly Caucasian, limiting generalizability of the finding to minorities. The problem with missing data from day 43 to day 56 may reflect 1) excessive subject burden of daily measures of fatigue and exercise, 2) increasing overall fatigue, or 3) a trend toward conserving energy to complete activities that were viewed as more important.

Conclusions

This study suggests the importance of short bouts of regular low-to-moderate intensity exercise to reduce fatigue in women with breast cancer receiving adjuvant chemotherapy. While contrary to standard practice, it appears that women with breast cancer who are regular exercisers should be encouraged to continue their exercise program and women who are not regular exercisers should be instructed to begin an exercise program. However, a randomized trial is needed to validate these results. Encouraging patients to exercise during cancer treatment to maintain and improve functional ability during chemotherapy appears to have a positive impact on fatigue, and functional ability (Dimeo et al 1997; Dimeo, Fetscher, Lange, Mertelsmann & Keul, 1997; Dimeo, Rumberger & Keul, 1998; Mock et al, 1997; Schwartz, 1997; 1998). This data suggests the dose of exercise to reduce fatigue may be of low-to-moderate intensity; with the greatest benefits observed in the first 10-20 minutes of exercise (more is better but the

returns in reduction of fatigue become less); and that daily exercise or at least exercise every-other day may be optimal.

Figure 1. Predicted reduction in fatigue level as a function of exercise duration

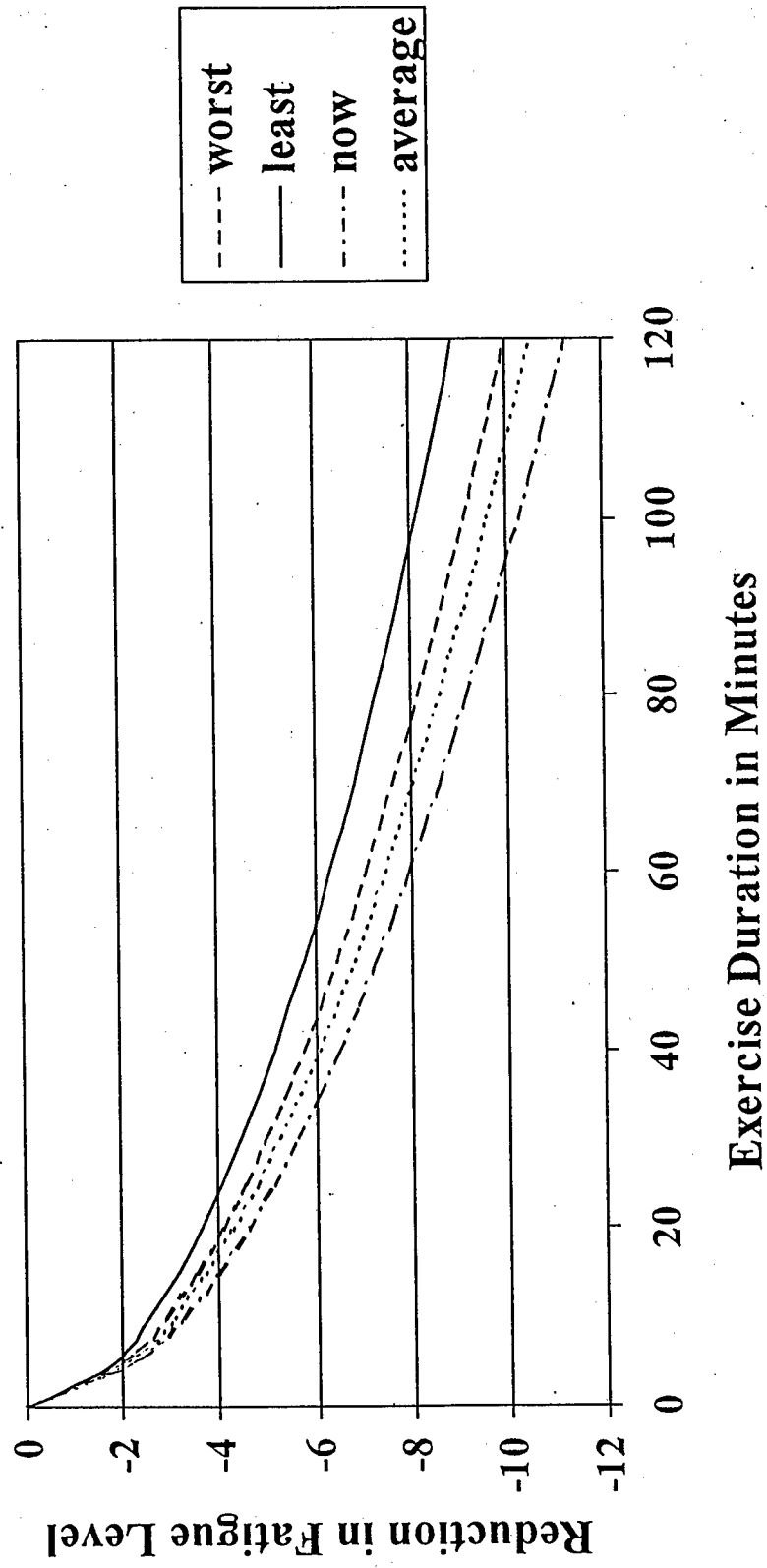


Table 1. Least squares means and standard errors for four measures of fatigue on no-exercise and exercise days.

	Worst fatigue	Least fatigue	Fatigue now	Average fatigue
Non-exercise day	50.98 (1.26)	22.81 (0.94)	47.11 (2.50)	36.90 (1.06)
Exercise day	46.01 (1.36)	18.14 (1.03)	40.66 (2.67)	31.65 (1.15)
p value	<.0001	<.0001	<.0001	<.0001

Table 2. Least squares means and standard errors for four daily measures of fatigue by number of minutes of exercise.

	Worst fatigue	Least fatigue	Fatigue now	Average fatigue
0 minute	50.99 (1.24)	22.85 (0.94)	47.11 (2.50)	36.89 (1.05)
1-30 minutes	47.87 (1.49)	18.69 (1.14)	42.30 (2.86)	33.55 (1.25)
31-60 minutes	43.43 (1.83)	17.29 (1.43)	36.16 (3.39)	28.47 (1.53)
>60 minutes	39.79 (3.01)	14.76 (2.44)	40.33 (5.33)	26.89 (2.56)
p value	<.0001	<.0001	.0005	<.0001

Table 3. Estimate and standard error of β_1 for Model 4.

Type of Fatigue	Estimate & Standard Error of β_1	Test for B_1
Worst fatigue	- 0.9096 (0.1631)	t=-5.58 p < .0001
least fatigue	- 0.8149 (0.1328)	t=-6.14 p < .0001
fatigue now	- 1.0243 (0.2931)	t=-3.49, p = .0005
average fatigue	- 0.9585 (0.1381)	t=-6.94, p < .0001

Table 4. Least squares means and standard errors for four measures of fatigue by total number of minutes of exercise.

	Worst fatigue	Least fatigue	Fatigue now	Average fatigue
0 minute	53.73 (2.07)	25.22 (1.57)	46.84 (4.11)	38.06 (1.76)
1-119 minutes	47.42 (2.13)	20.60 (1.65)	45.66 (3.98)	34.89 (1.82)
120-359 minutes	50.54 (2.10)	19.66 (1.62)	46.95 (3.79)	36.08 (1.78)
360-599 minutes	43.84 (2.80)	17.76 (2.16)	36.32 (4.94)	30.45 (2.38)
≥600 minutes	42.83 (3.45)	17.74 (2.64)	41.85 (6.21)	29.29 (2.93)
p value	.0088	.0326	.3243	.0443

Table 5. Definition of categorizations of days in terms of exercise on the current and previous day.

Group	Current Day	Previous Day	Number of Days
1	No exercise	No exercise	1,498
2	No exercise	Exercise	295
3	Exercise	No exercise	295
4	Exercise	Exercise	432

Table 6. Least squares means and standard errors for four measures of fatigue by the group defined by previous and current day of exercise.

Group ^a	Worst fatigue	Least fatigue	Fatigue now	Average fatigue
1	52.92 (1.37)	24.35 (1.04)	48.93 (2.69)	38.64 (1.16)
2	47.73 (1.57)	20.16 (1.21)	44.69 (2.95)	33.933 (1.31)
3	45.35 (1.56)	17.34 (1.19)	41.19 (2.98)	30.42 (1.20)
4	43.86 (1.62)	16.75 (1.25)	27.32 (3.09)	30.27 (1.39)
p value	<.0001	<.0001	<.0001	<.0001

a—groups defined in Table 5.

Table 7. Least squares means and standard errors for four measures of daily fatigue by caloric expenditure.

Caloric Expenditure	Worst fatigue	Least fatigue	Fatigue now	Average fatigue
0	47.33 (2.01)	20.93 (1.41)	44.65 (4.52)	32.94 (1.58)
1-119	46.55 (1.90)	16.41 (1.34)	40.13 (4.40)	32.82 (1.50)
≥ 120	44.04 (2.02)	16.48 (1.42)	32.13 (4.65)	28.94 (1.59)
p value	.3484	.0402	.1009	.0359

References:

Berstein M.L., Despars J.A., Singh N.P., Avalos K., Stansbury D. W. & Light, R.W. (1994). Reanalysis of the 12-minute walk in patients with chronic obstructive pulmonary disease. Chest, 105, 163-167.

Blesch, K.S., Paice, J.S.A., Wickham, R., Harte, N., Schnoor, D.K., Purl, S., Rehwalt, M., Kopp, P.L., Manson, S., Covey, S.B., McHale, M., & Cahill, M. (1991). Correlates of fatigue in people with breast or lung cancer. *Oncology Nursing Forum*, 18, 81-87.

Brooksoki, M.B., Pivarnik, J.M., & Morrow, J.R. (1991). Caltrac™ validity for estimating caloric expenditure in children [abstract]. Medicine and Science in Sports and Exercise, 23, S60.

Cooper, K.H. (1963). A means of assessing maximal oxygen uptake. Journal of the American Medical Association, 203, 133-138.

Dimeo, F.C., Fetscher, S., Lange, W., Mertelsmann, R., & Keul, J. (1997). Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. Blood, 90, 3390-3394.

Dimeo, F.C., Tilmann, M.H.M., Bertz, H., Kanz, L., Mertelsmann, R., & Keul, J. (1997). Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous stem cell transplantation. Cancer, 79, 1717-1722.

Dimeo, F.C., Rumberger, B.G., & Keul, J. (1998). Aerobic exercise as therapy for cancer fatigue. *Med Sci Sport Ex*, 30, 475-478.

Eaton, C.B., Reynes, J., Assaf, A.R., Feldman, H., Lasater, T., & Carlton, R.A. (1993). Predicting physical activity change in men and women in two New England communities. American Journal of Preventive Medicine, 9, 209-219.

- Fobair, P., Hoppe, R.T., & Bloom, L. (1986). Psychosocial problems among survivors of Hodgkin's disease. Journal of Clinical Oncology, 4, 805-814.
- Given, B., Given, C.W., Stommel, F., & Azzouz, F. (1999). Impact of initial treatment on change in physical functioning among older cancer patients. Proceedings 5th National Conference on Cancer Nursing Research, Newport Beach, CA.
- Gretebeck, R., Montoye, H. (1992). Variability of some objective measures of physical activity. Medicine and Science in Sports and Exercise 24, 1167-1172.
- Haymes, E.M., & Byrnes, W.C. (1991). Comparison of walking and running energy cost using the Caltrac and indirect energy calorimetry [abstract]. Med Sci Sport & Exercise, 23, S60.
- Hunter, G.R., Montoye, H.J., Webster, J.G., Demment, R., Ji, L.L., & Ng, A. (1989). The validity of a portable accelerometer for estimating energy expenditure in bicycle racing. J. Sport Med & Phys Fitness, 29, 218-222.
- Irvine, D., Vincent, L., Graydon, J.E., Bubela, N., & Thompson, L. (1994). The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. Cancer Nursing, 17, 367-78.
- Irvine, D.M., Vincent, L., Graydon, J.E., & Bubela, N. (1998). Fatigue in women with breast cancer receiving radiation therapy. Cancer Nursing, 21, 127-135.
- Jennrich, R.I., Schuchter, M.D. (1986). Unbalanced repeated measures models with structured covariance matrices. Biometrics, 42, 805-820.
- King, A.C. (1994) Community and public health approaches to the promotion of physical activity. Medicine and Science in Sport and Exercise, 26, 1405-12.

- King, A.C., Haskell, W.L., Taylor, B., Kraemer, H.C., & DeBusk, R.F. (1991). Group- vs home-based exercise training in healthy older men and women: A community based clinical trial. JAMA 266, 1535-42.
- King, A.C., Young, D.R., Oka, R.K., & Haskell, W.L. (1992). Effects of exercise format and intensity on two-year health outcomes in the aging adults (Abstract). The Gerontologist, 32, 190.
- King, K.B., Nail, L.M., Kraemer, K., Strohl, R., & Johnson, J. (1985). Patients' descriptions of the experience of receiving radiation therapy. *Oncology Nursing Forum*, 12, 55-61.
- MacVicar, M.G., & Winningham, M.L. (1986). Promoting the functional capacity of cancer patients. Cancer Bulletin, 38, 235-239.
- McAuley, E., Courneya, K.S., Rudolph, D.L., & Lox, C.L.L. (1994). Enhancing exercise adherence in middle-aged males and females. Preventive Medicine 23, 498-506.
- Mock, V., Burke, M.B., Sheehan, P., Creaton, E.M., Winningham, M.L., McKenney-Tedder, S., Schwager, L.P., & Leiberman, M. (1994). A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. Oncology Nursing Forum, 21, 899-907.
- Mock, V., Dow, K.H., Meares, C.J., Grimm, P.M., Dienemann, J.A., Haisfield-Wolfe, M.E., Quitasol, W., Mitchell, S., Chakravarthy, A. & Gage, I. (1997). An exercise intervention for management of fatigue and emotional distress during radiotherapy treatment for breast cancer. Oncology Nursing Forum, 24, 991-1000.

- Montoye, H.J., Washburn, R., Seavers, S., Eritt, A., Webster, A., & Nagle, F. (1983). Estimation of energy expenditure by portable accelerometer. Medicine and Science in Sports and Exercise, 15, 899-907.
- Nunnally, J.C., & Bernstein, I.H. (1994). Psychometric Theory (3rd ed.). New York, NY, McGraw Hill.
- Pambianco, G., Wing, R., & Robertson, R. (1990). Accuracy and reliability of the Caltrac™ accelerometer for estimating energy expenditure. Medicine and Science in Sports and Exercise, 22, 858-862.
- Pate, R.R., Pratt, M., Blair, S.N., Haskell, W.L., Macera, C.A., Bouchard, C., Buchner, D., Ettinger, W., Heath, G.W., King, A.C., Kriska, A., Leon, a.S., Marcus, B., Morris, J., Paffenbarger, R.S., Patrick, K., Pollock, M., Rippe, J.M., Sallis, J., & Eilmore, J.H. (1995). Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. Journal of the American Medical Association, 273, 402-407.
- Richardson, A., Ream, E., & Wilson-Barnett, J. (1998) Fatigue in patients receiving chemotherapy: patterns of changes. Cancer Nursing, 21, 17-30.
- Sallis JF, Buono MJ, Roby JJ, Carlson D, & Nelson JA. (1990). The Caltrac accelerometer as a physical activity monitor for school-age children. Medicine and Science in Sports and Exercise, 22, 698-703.
- SAS Institute, Inc. (1996). SAS/STAT Software: Changes and enhancements through release 6.11. Cary, NC, SAS Institute Inc.
- Schwartz AL. (1997) The relationship of exercise to fatigue and quality of life in women with breast cancer. Unpublished dissertation; University of Utah.

Schwartz, A.L. (1998). Patterns of exercise and fatigue in physically active cancer survivors. Oncology Nursing Forum, 25, 485-491.

Schwartz, A.L. (1998a). Effect of exercise on side effects, affect, and weight changes experienced by breast cancer patients receiving chemotherapy. Program/Proceedings of the American Society of Clinical Oncology, 16, 264.

Schwartz, A.L. (in press). Effect of exercise on the pattern of daily fatigue in women with breast cancer.

Steele, B. (1996). Timed walking tests of exercise capacity in chronic cardiopulmonary illness. Journal of Cardiopulmonary Rehabilitation, 16, 25-33.

Winningham, M.L., Nail, L.M., Burke, M.B., Brophy, L., Cimprich, B., Jones, L.S., Pickard-Holley, S., Rhodes, V., St. Pierre, B., Beck, S., Glass, E.C., Mock, V., Mooney, K.H., & Piper, B. (1994). Fatigue and the cancer experience: The state of the knowledge. Oncology Nursing Forum, 21, 23-36.

Young-McCaughan, S., & Sexton, D.L. (1991). A retrospective investigation of the relationship between aerobic exercise and quality of life in women with breast cancer. Oncology Nursing Forum, 18, 751-757.

ZuWallack, R.L., Patel, K., Reardon, J.Z., Clark, B.A., & Normandin, E.A. (1991). Predictors of improvement in the 12-minute walking distance following a six-week outpatient pulmonary rehabilitation program. Chest, 99, 805-808.

Effect of exercise on weight gain in women with breast cancer
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Privileged Communication

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Summary

Background: It is estimated that 175,000 women in the United States will be diagnosed with breast cancer in 1999. The majority of these women will be treated with surgery and/or chemotherapy and/or radiotherapy. Weight gain is a common side effect for women receiving adjuvant chemotherapy that is distressing and may have negative long-term implications for survival. The purpose of this study was to examine the effects of an exercise program on women with breast cancer receiving adjuvant chemotherapy. *Patients and methods:* Seventy-eight newly diagnosed women with breast cancer who were beginning adjuvant chemotherapy were enrolled in a home-based exercise study during the first 4 cycles of chemotherapy. Weight change, body mass index, anorexia, nausea, caloric expenditure during exercise and functional ability were recorded. *Results:* Women who adhered to the exercise program maintained their body weight, while nonexercisers steadily gained weight ($p < .05$). There were no differences in incidence or intensity of nausea or anorexia between the exercisers and nonexercisers. Women who exercised over the 4 cycles of chemotherapy improved their functional ability (23%) compared to the nonexercisers who showed significant declines in functional ability (-15%). *Conclusions:* Exercise may be an effective intervention to minimize weight gain in women with breast cancer receiving adjuvant chemotherapy. Preventing weight gain in these patients may be important in preventing recurrent disease and other comorbidities associated with excess weight.

Key Words: Breast cancer, exercise, weight gain, adjuvant chemotherapy

Background and Purpose

It is estimated that approximately 175,000 women in the United States will be diagnosed with breast cancer in 1999 (1). The majority of cases will be stage I or II and will be treated with surgery followed by chemotherapy and/or radiation therapy. Although the intent of adjuvant chemotherapy is to prevent recurrent disease, the treatment causes many distressing side effects, such as fatigue, alopecia, nausea, ovarian failure and weight gain. Weight gain, ranging from 2.5 to 6.2 kilograms, is commonly observed in women receiving adjuvant chemotherapy (2-4), with greater gains in weight observed in premenopausal women (5-7). Weight gain is a distressing side effect that affects a women's self esteem and body image (8) and predisposes breast cancer survivors to other morbidities such as diabetes mellitus and cardiovascular diseases (9). Several studies have noted an association between weight gain in breast cancer patients and the incidence of recurrence and death (5,10). A study of 646 breast cancer patients followed for a median of 6.6 years found that premenopausal women who gained more than 5.9 kilograms had a 1.5 time increased risk for recurrence, and 1.6 time increased risk for death from breast cancer than women who didn't gain as much weight (5). Clearly a significant problem, the mechanism of weight gain is unknown. Several causative factors have been suggested including inactivity (3, 11-13), decreased resting metabolic rate (3), hormonal changes (5,14), and overeating (10, 13, 15, 16).

While factors associated with weight gain in pre- and postmenopausal women receiving adjuvant chemotherapy were the focus of several articles in

past years (2-7, 9), no studies were found that examined the effect of an exercise intervention on weight gain. The purpose of this study was to examine the effect of aerobic exercise on weight gain in newly diagnosed women with stage I-III breast cancer receiving either (AC) or cyclophosphamide, methotrexate and fluorouracil (CMF). The research hypothesis was that women who exercised would maintain their body weight during the first four cycles of adjuvant chemotherapy.

Method

A pretest-posttest one group design was used to explore the effect of exercise on weight gain in women with breast cancer who did and did not adhere to a home-based exercise program.

Sample: Seventy-eight newly diagnosed women with histologically confirmed infiltrating ductal carcinoma were enrolled in the 8-week exercise study. Women were invited to participate who were over 18 years of age, able to speak and read English, ambulatory, and chemotherapy and radiotherapy naïve. None of the women had comorbidities, such as cardiovascular disease, movement limiting arthritis, or pulmonary diseases, that precluded beginning an exercise program. Women with a history of psychiatric illness were excluded.

Seventy-one women completed the study. The majority of women in this study were married (70%), Caucasian (93%), and were employed either full-time or part-time (51%). The mean age of the sample was 47 years old (range 27-71). While this group of women was well educated (80% had attended some college), the majority did not report exercising regularly (58%). The women who

were regular exercisers reported exercising 4 days a week for an average of 39 minutes per session. All women had completed surgery at least 21 days before study entry. Women were primarily being treated for stage II and III breast cancer (81%), and were receiving either AC (57%), or CMF (43%).

Measures: Demographics. Demographic data were obtained on age, ethnicity, marital status, education and previous exercise behavior. Clinical information including stage of disease, chemotherapy regimen and number of days since surgery was obtained by chart review.

Functional ability. A pretest and posttest 12-minute walk was used as a measure of functional ability. The 12-minute walk is a commonly used, clinically relevant measure of functional ability (17, 18). It is highly correlated with oxygen uptake (19). The women were instructed to walk as fast as they could for 12-minutes. Encouragement was limited to the final 2 minutes of the test. Women who increased their functional ability at posttest were classified as exercisers. This categorization was clear. Women either increased or decreased the distance covered in the 12-minute walk.

Activity measure. Caloric expenditure during exercise was measured using a Caltrac™ accelerometer. The device is worn on the side of the waist on the dominant side of the body. The Caltrac™ has demonstrated inter-instrument reliability (20), test-retest reliability (21) and validity (22). Women used the Caltrac™ during the 12-minute walks and were given a Caltrac™ to use when they exercised at home. Instruction was provided on how to use the Caltrac™, a

user's information guide, and a 24-hour number to call if the woman experienced problems with the Caltrac™. Subjects recorded number of calories expended during each exercise session in exercise logs.

Self-reported exercise. Exercise logs were used to record exercise frequency, intensity, duration and type of exercise the women engaged in. Women maintained these logs daily for the duration of the study. Telephone calls, placed by the research assistants, were used to remind women to complete the exercise logs and mail them to the study site at the end of each week.

Body Weight Weight, measured in kilograms, was obtained before each dose of chemotherapy. Weight was measured on a balance beam scale that was balanced and measured weight in 0.1 kilogram increments. Women were weighed in clothing by the clinic nurses on the same scale. The combined measure of height and weight was used to calculate body mass index (kg/m^2).

Side Effects The Side Effect Symptom Checklist was used to determine presence and intensity of anorexia and nausea. Patients were interviewed by telephone each week and asked if they had experienced decreased appetite or nausea, and if so how severe it was on a 5-point scale (0 = not present to 5 = severe). The Side Effect Symptom Checklist is a well tested instrument that is commonly used in cancer trials (23).

Procedure: Human subjects approval was obtained before the study began.

Eligible women were identified by their physicians. Women were recruited from a University cancer center and a community oncology practice in the Intermountain

West. The study was explained to the women and written informed consent was obtained. Pretest measures were collected before the first dose of chemotherapy.

All eligible and consenting women were asked to follow an 8-week, home-based aerobic exercise program. Women were instructed to begin the exercise program one to two days after receiving their first dose of chemotherapy. The exercise prescription included 15-30 minutes of exercise 4 days a week at an intensity that was limited by symptoms such as pain and fatigue. To improve adherence, women were asked to engage in an aerobic exercise that they enjoyed. Instruction was provided on the use of the Caltrac™ accelerometer. All women received weekly follow-up telephone calls to encourage exercise adherence, determine barriers to exercise, record side effects and remind women to complete and return their exercise logs.

Analysis

Descriptive analyses are presented for the sample, functional ability, energy expenditure, and body weight. T-tests and analysis of variance were used to explore differences in body weight, and side effects experienced by exercisers (women who improved in functional ability from baseline to posttest) and nonexercisers (women who declined in functional ability from baseline to posttest).

Results

Women who did not adhere (N=29) to the exercise program demonstrated declines in functional ability of almost 23% from pretest (Mean = 3291 ft, SD =

633) to posttest (Mean = 2649ft, SD = 1010). The women who adhered to the exercise program (N=42) demonstrated a 15% increase in functional ability from pretest (Mean = 3407ft, SD = 692) to posttest (Mean = 34856 ft SD=611). The differences in functional ability between the exercisers and nonexercisers were statistically significant ($t=-7.75$, df 69, $p<.000$). The women who adhered to the exercise program reported exercising an average of 136 minutes a week (SD = 97) or 33 minutes per exercise session (SD = 22). Caloric expenditure during each exercise session averaged 77 kcals (SD = 51). There were no differences in the women who did and did not adhere to the exercise program by age, marital status, level of education, stage of disease, or type of chemotherapy.

Women who did not adopt the exercise program weighed more at baseline than the women who exercised (Mean = 76.8 kg, SD= 18; Mean = 68.2 kg, SD = 10.9, respectively), and had greater body mass index (Mean = 23.1, SD = 4.7; Mean = 20.5, SD = 3.1). The nonexercisers were observed to steadily increase weight over the first four cycles of chemotherapy (Table 1). When controlling for baseline weight, analysis of variance demonstrated significant differences in weight gain between the two groups at the third and fourth chemotherapy (Table 2).

Anorexia scores, for both groups, peaked after the first chemotherapy (exercisers Mean = 1.5, SD= 2.1; nonexercisers Mean = 1.6, SD = 1.9) and reached a low in the third week of the second cycle of chemotherapy (exercisers Mean = 0, SD= 0; nonexercisers Mean = 0.87, SD = 1.1). Nausea scores peaked after the third chemotherapy (exercisers Mean = 2.5, SD= 3.5;

nonexercisers Mean = 2.2, SD = 2.0) and were lowest at the end of the third week of the third cycle of chemotherapy (exercisers Mean = 0.5, SD = 0.7; nonexercisers Mean = 2.2, SD = 1.2). No significant differences in incidence or intensity of either anorexia ($p > 0.2$ at all points in time) or nausea ($p > 0.2$ at all points in time) were observed by exercisers and nonexercisers. No differences were observed in anorexia or nausea by type of chemotherapy ($p > 0.3$).

Discussion

Exercise appears to have an effect on maintenance of body weight in women with breast cancer who are receiving adjuvant chemotherapy. Although the energy expended by these women was modest and reflects low intensity exercise, the observed benefits in functional ability were substantial. Physical activity levels have been observed to significantly decrease during chemotherapy (3, 11), which may account for the increases in weight observed among the women who did not exercise.

Weight gain in women with breast cancer receiving adjuvant chemotherapy is associated with a number of other factors. Some researchers have suggested that weight gain may simply be related to the disease process and not related to the treatment (24). This idea may explain why there were no differences in weight gain between the two groups by severity of anorexia, nausea, or type of chemotherapy. Dietary intake is often suggested to be a cause of weight gain, but this study did not observe differences in appetite between those who exercised and those who did not. The lack of difference in appetite

strengthens the argument that differences in weight may be related to differences in physical activity and total energy expenditure (3).

Length of treatment is also associated with weight gain (2). Women who did not exercise gained an average of 3.2 kilograms, which exceeds the weight gains observed in other studies of women receiving either CMF or CMF with prednisone over much longer periods of time (5, 25). The reasons for the greater weight gain observed in this sample are unclear. Perhaps women gain weight more rapidly during the first few cycles of chemotherapy than in later cycles?

Fatigue is recognized as the most common and distressing side effect of cancer treatment (26). Exercise has consistently been observed to decrease cancer-related fatigue (18, 27-33). The combination of reduced fatigue and increased energy expended in exercise may provide the best explanation of the differences in weight gain observed among women in this sample.

Findings from several studies with large sample sizes have observed an increased risk of recurrence among women who gain weight following chemotherapy (5, 10, 24, 34). Although these results are not conclusive and several smaller studies have observed opposing results (6, 24, 35), the observations are distressing. The association between increased weight gain and recurrence and death have particular significance for younger, premenopausal women who tend to demonstrate the greatest weight gains (5-7) and often have more aggressive tumor histologies. Although the relationship between weight gain and serum lipid levels have not been studied in these women, excessive weight gain and obesity confer other health risks that should not be overlooked.

These risks include diabetes, cardiovascular disease, orthopaedic and emotional problems (36-40). The risk of coronary artery disease is further increased for women who receive anthracycline-based therapy (41).

The combination of maintaining weight and improving functional ability during chemotherapy may be an unusual outcome to expect for women with breast cancer receiving adjuvant chemotherapy. However, a clinical paradigm change may be evolving as preliminary evidence mounts in support of exercise as an intervention to minimize weight gain, reduce fatigue, improve functional ability, mood and diseases of disuse that often accompany cancer treatment (18, 27-33). Exercise has also been suggested to have a protective effect against the development of breast cancer in young women (42), and older women (43, 44) and is clearly linked to reducing risks for other co-morbid conditions that decrease quality of life, and cause significant morbidity, mortality and expense (45-47).

This study has several limitations in addition to the one group design. These include a short follow-up period and the inability to differentiate women by menopausal status. Menopausal status is an important consideration because premenopausal women have been observed to gain more weight than menopausal women (4), and weight gain in postmenopausal women is associated with an increased risk for breast cancer (48). Further study is needed to determine the mechanisms of weight gain, and effective interventions to improve breast cancer survivors' quality and quantity of life.

Table 1. Weight (in kilograms) over 4 cycles of chemotherapy.
Exerciser Nonexerciser

	M (kg)	SD	M (kg)	SD
Baseline	68.0	10.9	76.6	18.1
2 nd chemo	66.2	11.8	74.4	16.3
3 rd chemo	65.8	10.9	78.0	18.1
4 th chemo	68.0	12.7	79.8	19.9

Table 2. Differences in weight between exercisers and nonexercisers.

	Sum Squares	df	F	p
2 nd chemo				
between	1824	1	2.9	.10
within	14700	24		
total	16524	25		
3 rd chemo				
between	3445	1	6.2	.02
within	10062	18		
total	13508	19		
4 th chemo				
between	5828	1	6.6	.02
within	30082	34		
total	35909	35		

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References

1. Landis, S.H., Murray, T., Bolden, S., Wingo, P.A.: Cancer Statistics, 1999. *CA: A Cancer J for Clinicians*, 49: 8-31, 1999.
2. Bonadonna, G., Valagussa, P., & Rossi, A.: Ten year experience with CMF-based adjuvant chemotherapy in resectable breast cancer. *Breast Cancer Res Treat* 5: 95-115, 1985.
3. Demark-Wahnefried, W., Hars, V., Conaway, M.R., Havlin, K., Rimer, B.K., McElveen, G., & Winer, E.P.: Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. *Amer J Clin Nut*, 65: 1495, 1997.
4. Hoskin, P.J., Ashley, S., Yarnold, J.R.: Weight gain after primary surgery for breast cancer: effect of tamoxifen. *Breast Cancer Res. Treat.* 22:129-132, 1992.
5. Camoriano, J.K., Loprinzi, C.L., Ingle, J.N., Therneau, T., Krook, J., & Veeder, M.: Weight change in women treated with adjuvant therapy or observed following mastectomy for node positive breast cancer. *J. Clin Oncol* 8: 1327-1334, 1990.
6. Heasman, K.Z., Sutherland, H.J., Campbell, J.A., Elhakim, T., & Boyd, N.: Weight gain during adjuvant chemotherapy for breast cancer. *Breast Cancer Res Treat*, 5: 195-200, 1985.
7. Tormay, D.C., Taylor, S.G., & Kalish, L.A.: Adjuvant systemic therapy in premenopausal and postmenopausal women with node-positive breast cancer, in *Adjuvant Therapy of Cancer* (ed 4). Philadelphia, PA, Grune & Stratton, pp 359-368, 1996.

8. Knobf, M.K., Mullen, J.C., Xistris, D., Moritz, D.A.: Weight gain in women with breast cancer receiving adjuvant chemotherapy. *Oncol Nurs Forum*, 10: 28-34, 1983.
9. Demark-Wahnefried, W., Winer, E.P., & Rimer, B.K.: Why women gain weight with adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 11: 1418-1429, 1993.
10. Chemblowski, R.T., Weiner, J.M., Reynolds, R., Luce, J., Bulcavage, L., Bateman, L.: Long-term survival following relapse after 5-FU but not CMF adjuvant breast cancer therapy. *Breast Cancer Res Treat* 7: 23-29, 1986.
11. Frumkin, L.R.: Weight gain in women receiving adjuvant chemotherapy for breast cancer. (Questions and answers). *JAMA*, Sept 18, 276: 855, 1996.
12. Albahes, D., Conway, J.M., Taylor, P. R., Moe, P.W., Judd, J. Validation and comparison of eight physical activity questionnaires. *Epidemiology* 1:65-71, 1990.
13. Huntington, M.O. Weight gain in patients receiving adjuvant chemotherapy for carcinoma of the breast. *Cancer* 56:472-474, 1985.
14. Zumoff, B., Gorzynski, J.G., Katz, J.L. Weiner, H., Levin, J., Holland, J., Fukushima, D.K. Nonobesity at the time of mastectomy is highly predictive of 10-year disease free survival in women with breast cancer. *Anticancer Res* 2:59-62, 1982.
15. Mukhopadhyay, M.G., & Larkin, S. Weight gain in cancer patients on chemotherapy. *Proc Am Soc Clin Oncol* 5:254, 1986 (abstr 992).

16. Grindel, C.G., Cahill, C.A., Walker, M. Food intake of women with breast cancer during their first six months of chemotherapy. *Onco Nurs Forum* 16:401-407, 1989.
17. Steele B.: Timed walking tests of exercise capacity in chronic cardiopulmonary illness. *J Cardiopulm Rehab* 16: 25-33, 1996.
18. Mock V, Burke MB, Sheehan P, Creaton EM, Winningham ML, McKenney-Tedder S, Schwager, L.P., & Liebman, M.: A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. *Onc Nurs Forum*, 21, 899-907, 1994.
19. Cooper KH. A means of assessing maximal oxygen uptake. *JAMA* 203:133-38, 1968.
20. Pambianco, G. Wing, R., & Robertson, R.: Accuracy and reliability of the Caltrac accelerometer for estimating energy expenditure. *MSSE* 22: 858-862, 1990.
21. Washburn, R.A., & LaPorte, R.E.: Assessment of walking behavior: Effect of speed and monitor position on two objective physical activity monitors. *Res Quarterly Ex Sport* 59: 83-85, 1988.
22. Montoye, H.J., Kemper, H.C., Saris, W.H., & Washburn, A. *Measuring physical activity and energy expenditure*. Champaign, IL: Human Kinetics, 1996.
23. King, K.B., Nail, L.M., Kraemer, K., Strohl, R., & Johnson, J.: Patients' descriptions of the experience of receiving radiation therapy. *Oncol Nurs Forum*, 12: 55-61, 1985.

24. Goodwin, P.A., Panzarella, T., & Boyd, N.F. (1988). Weight gain in women with localized breast cancer – A descriptive study. *Breast Cancer Res. Treat.* 11, 59-66.
25. Smigel, K. : Poor prognosis? *J. Natl Cancer Inst* 82, 349-350, 1990.
26. Cella, D. Peterman, A., Passik, S., Jacobsen, P., Breitbart, W. Progress toward guidelines for the management of fatigue. *Oncology* 12:369-77, 1998.
27. Dimeo, F., Rumberger, B.G., & Keul, J.: Aerobic exercise as therapy for cancer fatigue. *MSSE* 30: 475-478, 1998.
28. Dimeo FC, Tilmann MHM, Bertz H, Kanz L, Mertelsmann R, Keul J.: Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous stem cell transplantation. *Cancer*, 79: 1717-22, 1997.
29. Dimeo FC, Fetscher S, Lange W, Mertelsmann R, Keul J.: Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood*, 90: 3390-94, 1997.
30. Mock V, Dow KH, Meares CJ, Grimm PM, Dienemann JA, Haisfield-Wolfe ME, Quitasol, W., Mitchell, S., Chakravarthy, A., & Gage, I.: An exercise intervention for management of fatigue and emotional distress during radiotherapy treatment for breast cancer. *Oncology Nursing Forum*, 24: 991-1000, 1997.
31. Schwartz A.L.: Patterns of exercise and fatigue in physically active cancer survivors. *Oncol Nurs Forum* 25: 485-491, 1998.

32. Schwartz, A.L.: Fatigue mediated the effects of exercise on quality of life. *Quality of Life Research* accepted, 1999.
33. Schwartz, A.L., Mori, M., Gao, R., Nail, L.M., King, M.E., & Madsen, S.: Exercise Dose and Fatigue: Day to Day Variation in Women with Breast Cancer. *Nursing Research* in review, 1999.
34. Chemblowski, R.T., Rose, D., Buzzard, I.M., Blackburn, G.L., Insull, W., Grosvenor, M., Elashoff, R., & Wynder, E.L.: Adjuvant dietary fat reduction in postmenopausal breast cancer patient management. *Breast Cancer Res Treat* 20: 73-84, 1991.
35. DeConti, R.C. Weight gain in adjuvant chemotherapy of breast cancer. *Proc Am Soc Clin Oncol* 1:73 (abstr C-279), 1982.
36. Danesh, J., Muir, J., Wong, Y., Ward, M., Gallimore, J.R., Pepys, M.B. : Risk factors for coronary heart disease and acute-phase proteins. A populations-based study. *Eur Heart* , 20: 954-59, 1999.
37. Halle, M., Berg, A., Garwers, U., Baumstark, M.W., Knisel, W., Grathwohl, D., Konig, D., Keul, J.: Influence of 4 weeks' intervention by exercise and diet on low-density lipoprotein subfractions in obese men with type 2 diabetes. *Metabolism*, 48:641-4, 1999.
38. Mills, J.K., & Andrianopoulos, G.D.: The relationship between childhood onset obesity and psychopathology in adulthood. *J Psychol*, 127:547-51, 1993.
39. Perreault, S., Dorias, M., Coupal, L., Paradis, G., Joffres, M.R., & Grover, S.A.: Impact of treating hyperlipidemia or hypertension to reduce the risk of death from coronary artery disease. *CMAJ* 160: 1449-55, 1999.

40. Wadden, T.A., & Stunkard, A.J.: Social and psychological consequences of obesity. *Ann Int Med* 103: 1062-7, 1985.
41. Hancock, S.L. : Cardiac toxicity after cancer therapy. *Research Issues in Cancer Survivorship*, March 9-10, 1998.
42. Bernstein, L., Henderson, B.E., Hanish, R., Sullivan-Halley, J., & Ross, R.K.: Physical exercise and reduced risk of breast cancer in young women. *J. Natl Cancer Inst*, 86, 1403-8, 1994.
43. Coogan, P.F., Newcomb, P.A., Clapp, R.W., Trentham-Deitz, A., Baron, J.A., & Longnecker, M.P.: Physical activity in usual occupation and risk of breast cancer (United States). *Cancer Causes Control* 8: 626-31, 1997.
44. McTiernan, A., Stanford, J.L., Weiss, N.S., Daling, J.R., & Voigt, L.F.: Occurrence of breast cancer in relation to recreational exercise in women age 50-64 years. *Epidemiology*, 7: 598-604, 1996.
45. Blair, S.N. Kohl, H.W., Barlow, C.E.: Changes in physical fitness and all-cause mortality. *JAMA* 273:1093-1098, 1995.
46. Paffenbarger, R.S. Hyde, R.T., & Wing, A.L.: Physical activity and incidence of cancer in diverse population: a preliminary report. *Amer J Clin Nut* 45:312-317, 1987.
47. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, Buchner, D., Ettinger, W., Heath, G.W., King, A.C., Kriska, A., Leon, A.S., Marcus, B.H., Morris, J., Paffenbarger, R.S., Patrick, K., Pollock, M.L., Rippe, J.M., Sallis, J., Wilmore, J.H.: Physical activity and public health: A recommendation from the

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Centers for Disease Control and Prevention and the American college of Sports
Medicine. *JAMA* 273: 402-407, 1995.

48. Avoiding adult weight gain helps women reduce breast cancer risk. *Amer
Med News* Nov 10, v 40: 22, 1997.

Daily Fatigue Pattern and effect of exercise in women with breast cancer.
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Privileged Communication

Daily Fatigue Pattern and Effect of Exercise
in Women with Breast Cancer

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Abstract

Purpose: Cancer treatment-related fatigue is a common and disruptive side effect of chemotherapy. Exercise is an intervention proposed to reduce fatigue in cancer patients. The purpose of this study was to describe the patterns of fatigue in women with breast cancer women who did and did not exercise while receiving adjuvant chemotherapy.

Description of Study: Women received instruction to follow an 8-week home-based exercise program and maintain daily exercise and fatigue diaries. Functional ability (12-minute walk) was measured at pretest and posttest.

Results: Several distinct patterns of fatigue emerged. The most common pattern of fatigue after chemotherapy demonstrated a sharp rise in fatigue. However, several women demonstrated a chaotic pattern with erratic and wide swings in their fatigue throughout the entire study period. Women who adopted exercise experienced fewer days of fatigue above their baseline and more days of fatigue below baseline. Women who did not exercise experienced more days of high fatigue and fewer days of low fatigue.

Clinical Implications: Exercise appears to reduce fatigue and may help women recognize their pattern of fatigue. Exercise may reduce the intensity of fatigue by reorganizing women's interpretation of fatigue.

Key Words: fatigue, exercise, breast cancer, visual analog scale

Background and Purpose

Cancer treatment-related fatigue is a common and distressing symptom among cancer patients during and after treatment (Nail & Jones, 1995; Schwartz, 1998). Patients describe the experience of cancer treatment-related fatigue (fatigue) as being different from the fatigue experienced before cancer. The fatigue of cancer is characterized as being a more intense, chronic, disruptive sensation that is unrelieved by rest (Dean & Ferrell, 1995; Schwartz, 1998). Cella and colleagues (1998) have proposed a definition of fatigue that describes the symptom, common features, and major characteristics. Fatigue is defined as an abnormal condition that persists for two or more weeks and occurs on most days. Common features may include reduced motivation and interest in activities, exhaustion, apathy, generalized weakness, sleep abnormalities, irritability and sadness. Major characteristics include: reduced energy that is disproportionate to activity level, distress often associated with reduced physical or intellectual performance, causally related to the disease or its treatment, and not related to a psychiatric disorder.

The incidence of fatigue, when comparing across types of treatment and type and stage of cancer ranges from 40% and 100% (Irvine, Vincent, Bubela, Thompson, & Graydon, 1991; Nail & Winningham, 1995; Vaders & Kemp, 1995; Richardson & Ream, 1996). Fatigue negatively impacts all aspects of quality of life (Pickard-Holley, 1991; Post-White & Schroeder, 1997; Vogelzang et al, 1997). While several theories have been proposed to explain fatigue (Bruera & MacDonald, 1988; St. Pierre, Kasper & Lindsey, 1992) and predict the response to fatigue (Piper, Lindsey & Dodd, 1987; Winningham et al, 1994), none provide a parsimonious explanation of the phenomenon or its etiology.

Exercise plays a significant role in the prevention of disease and in the rehabilitation and control of disease progression in many populations of chronically ill

patients (Blair et al., 1995; Lorig et al, 1999; Paffenbarger et al, 1993; Pate et al, 1995), and is an intervention suggested to minimize fatigue in cancer patients (Dimeo, 1997, 1998; Mock, 1994, 1997; MacVicar & Winningham, 1986; Schwartz, 1998). Exercise interventions for people with diseases associated with inactivity may retard debilitation, weakness, fatigue and declines in functional ability and quality of life. As treatment and survival rates improve, developing interventions to control fatigue during cancer treatment becomes increasingly important. In a review of the literature, no studies were found that examined the daily pattern of fatigue in women with breast cancer who participated in an exercise program. The purpose of the study was to examine the pattern and amount of fatigue over 3 cycles of chemotherapy in women with breast cancer receiving adjuvant chemotherapy and compare differences between women who adhered to an exercise program and women who did not.

Method

A pretest-posttest one group design was used to study the daily pattern of fatigue in women with breast cancer who did and did not adhere to an 8-week home-based exercise program.

Sample: Thirty-one newly diagnosed women with stage I-IV breast cancer were enrolled in the 8-week exercise study. Women were invited to participate who were chemotherapy naive, over 18 years of age, ambulatory, able to speak and read English, and without musculoskeletal or cardiorespiratory diseases that would preclude exercise. Women with mental illness were excluded.

Twenty-seven women completed the study. The majority of women in this study were married (74%), Caucasian (87%), and were employed either full-time (55%) or part-time (19%). The mean age of the sample was 47 years old (range 35-57). While

this group of women was well educated (77% had attended some college), the majority were not regular exercisers (55%). The women who were regular exercisers reported exercising 4 days a week for an average of 42 minutes per session.

All of the women had surgery at least 21 days before study entry. Women were primarily being treated for stage II and III breast cancer (70%). The combination of doxorubicin and cyclophosphamide (74%) was the most common chemotherapy regimen, followed by cyclophosphamide, methotrexate and fluorouracil (23%), and vinorelbine (3%).

Measures: Demographics. Demographic data included age, ethnicity, marital status, education and previous exercise behavior. Clinical information regarding stage of disease, chemotherapy regimen and number of days since surgery were obtained by chart review.

Functional ability. The 12-minute walk was used as a measure of functional ability at pretest and posttest. The test is highly correlated with oxygen uptake (Cooper, 1968) and is a commonly used measure of functional ability (Steele, 1996; Mock et al, 1994). The women were asked to walk as fast as they could for 12-minutes and were encouraged only in the final 2 minutes of the test. Women who increased the 12-minute walk distance at posttest, increased their functional ability and were classified as exercisers.

Exercise intensity. Caltrac™ accelerometers were used to measure energy expended during exercise, which reflects exercise intensity. The Caltrac™ is a small pager-like device that is worn on the side of the waist on the dominant side. It has demonstrated inter-instrument reliability (Pambianco et al 1990), test-retest reliability (Washburn et al 1988) and validity (Montoye, et al 1996). The women wore the Caltrac™ during the 12-

minute walks and were given a Caltrac™ to use at home when they exercised. Women received instruction on how to use the Caltrac™, a user's information guide, and a 24-hour number to call if they had problems with the device. Subjects records of calories expended during exercise were recorded in the exercise logs.

Self-reported exercise and fatigue. Exercise logs were maintained for each day of exercise. The women recorded frequency, intensity, duration and type of exercise they engaged in. This information was recorded on the same form used for the fatigue logs.

Visual Analogue Scales (100mm) of the average and worst fatigue experienced each day were recorded in logs. Women were asked to make a mark though the line to indicate their level of fatigue on the average and at its worst in the past 24-hours from "no fatigue at all" to "incapacitated by fatigue". Visual analogue scales of fatigue (VAS-F) have been used in previous studies of fatigue in cancer patients (Mock et al 1994; Blesch et al, 1991; Schwartz, 1998a). The women were instructed to complete the measures at the same time each night before going to bed. Consistency in measurement time and regularity of recording the data were methods used to reduce time variability in the fatigue measurement and to increase compliance with data recording.

Procedure: Human subjects approval was obtained before the study commenced. Women were recruited from a University cancer center and a community oncology practice. Potential eligible subjects were identified by their physician. The study was explained to the women, written informed consent was obtained, pretest measures were collected, and instruction was provided on the exercise program and use of the Caltrac™ before the first dose of chemotherapy. The women were asked, each day of the study, to record their worst and average level of fatigue and their exercise frequency, duration and

intensity. These measures were obtained nine weeks later, before the 4th dose of chemotherapy, at posttest.

All eligible and consenting women received instruction to follow a low intensity, 8-week, home-based aerobic exercise program. The exercise program was designed to accommodate to individual levels of functional ability. During chemotherapy weeks, the exercise dose (duration and intensity of exercise) was reduced. Subjects adopted the program at varying levels, and were instructed to exercise at an intensity that did not provoke symptoms such as, pain, fatigue, or nausea.

Analysis

Descriptive analyses are presented for the sample, functional ability and energy expenditure. Graphical displays of subjects' daily plots of worst & average fatigue were examined for each subject and categorized according to type of pattern. Exercisers were defined as the women who improved in functional ability from baseline to posttest. The exercisers were compared to the nonexercisers, the women who declined in functional ability from baseline to posttest. The extreme variability in the data made analysis by more standard techniques, such as individual regression analysis or time series analysis, not feasible. When describing the different patterns of fatigue, the number of women in each category varies because not all women demonstrated the same pattern of fatigue.

Results

Exercise: While the majority of women were not regular exercisers at baseline, 60% of the women adopted the exercise program as demonstrated by increasing their 12-minute walk distance at posttest and reported exercise in their daily logs. Baseline walking distance ranged from 2244-4905 ft ($M=3702$, $SD=474.73$) and at posttest the

distance ranged from 1763-5747 ft ($M=3685$, $SD=782.22$). Functional ability increased 10% (range=1-24%) in those who adopted exercise ($N=16$). A mean decline of 16% (range=2-37%) was observed in women who did not adopt exercise ($N=11$). Women who adhered to the exercise program exercised an average of 23 minutes, 4 days a week, expending an average of 134 calories per exercise session, as measured by the Caltrac™ accelerometer. No differences were observed in age, stage of disease or type of chemotherapy between those women who adopted the exercise program and those who did not.

Patterns of peak fatigue in the days following chemotherapy

Average daily fatigue and worst fatigue on each day were plotted over time to determine patterns of fatigue after chemotherapy. The most common pattern across all plots was a rapid increase in both worst and average fatigue after chemotherapy. This pattern is illustrated by the subject's report of average fatigue shown in Figure 1. Fatigue remained elevated for 3-4 days following chemotherapy, and then slowly trended downwards. Two subjects demonstrated a variation of this pattern with a prolonged elevation in fatigue lasting 10 days after chemotherapy. Another pattern showed a 1-4 day delayed onset of peak fatigue after chemotherapy (Figure 2).

Fatigue is often reported to peak during the hematologic nadir period (Irvine et al, 1994; Pickard-Holley, 1991; Richardson, 1998). Previous studies have not examined the daily pattern of fatigue over several cycles of chemotherapy. In looking at the graphical displays of daily fatigue only two of the plots show a clear pattern of fatigue consistent with a rise in fatigue during the nadir (Figure 1). In figure 1, the fatigue rises on day 15 and again on day 35. This increase in fatigue is brief, only lasting one day, and not as high as the fatigue experienced after receiving chemotherapy. Other patterns

showed increased fatigue at the nadir, but this was part of an irregular pattern across all days.

Some subject's fatigue was not associated with chemotherapy or adverse events. These patterns were extremely variable, lacked organization, and were somewhat chaotic. VAS-F scores on these plots ranged from 0-100, and this amplitude of variability did not dampen over time (Figure 4). This woman's pattern of fatigue did begin to show more order and organization over the three cycles of chemotherapy.

Fatigue was associated with adverse events: neutropenic fever, minor infections, bone marrow biopsy, and line placement. The seven women who experienced adverse events demonstrated a sharp increase in their average fatigue during the adverse event that lasted between 2 and 10 days (Figure 3). The level of worst fatigue that women experienced during this time continued to be elevated as long as 12 days following the adverse event.

Patterns of fatigue over the three cycles of chemotherapy

The most frequent pattern showed declines in the highest levels of average fatigue with each cycle of chemotherapy. Figure 5 clearly illustrates the increase in fatigue with each chemotherapy dose. The decrease in peak fatigue levels is observed during the second and third cycle of chemotherapy. There also was a gradual increase in the lowest levels of fatigue. In general, the range of fatigue narrows over time. Ten women who were exercisers showed this pattern of fatigue over time. In contrast, four subjects who did not adhere to the exercise program had increases in the highest levels of fatigue with each cycle of chemotherapy.

The measure of worst fatigue showed a similar downward trend and narrowing range in fatigue for exercising subjects. Figure 6 shows the narrowing swings of fatigue over time and increasing intensity of the lower levels of fatigue over time. The

relationship of these patterns of fatigue scores over time and adherence to the exercise program was examined using Chi-square (Table 1). Subject's who adhered to the exercise program were significantly more likely to have reduced worst fatigue scores over the three cycles of chemotherapy than nonexercisers. There was a trend for the same result for average daily fatigue scores.

Number of days fatigue BELOW baseline by chemotherapy cycle

To determine the number of days of fatigue below baseline by chemotherapy cycle, or number of good days, we counted the number of days each woman rated her current fatigue lower than her baseline rating. The percent of good days was calculated by dividing the number of days below baseline by the total number of days in the cycle or the number of data points recorded for that cycle. While this method maximized the data, it was limited in several ways. First, some data points were missing, which created the potential bias that the days of missing data may have been days when women experienced extremely high or low fatigue. Second, fatigue was more often recorded in the days following chemotherapy, potentially causing a bias of capturing higher periods of fatigue. Third, a floor effect was observed; with some women recording zero fatigue at baseline and never scoring zero again. This made the calculation of number of days below baseline impossible for these women. Lastly, women were less compliant in recording daily fatigue during the last 2 weeks of the study, which created a bias of increased number of days of high fatigue in the last cycle of chemotherapy.

The pattern of average fatigue revealed that women who exercised had more good days (67%), than for the women who did not exercise (16%). The results for the measure of worse fatigue were similar. Women who exercised had 67% good days compared to 25% for nonexercisers. However, these differences were not significant ($\chi^2 = .25$ for average fatigue and 2.13 for worst fatigue, $p > .05$). Only 2 nonexercisers

showed an increase in the number of good days as indicated by worse fatigue scores below baseline. The percent of days below baseline at each cycle shows a decrease in the number of days that average and worst fatigue were below baseline among women who did not adopt exercise (Table 2). This suggests that the nonexercisers experienced more days of high fatigue than the exercisers.

Number of days fatigue ABOVE baseline by chemotherapy cycle

Calculation of the number of days above baseline (bad days) was similar to the previous calculation except that it relied on counting the number of days each woman recorded fatigue above baseline and dividing the total number of days in the cycle or the number of data points recorded for that cycle. The limitations discussed in the previous section apply to this exploratory analysis too, with the exception that a ceiling effect was observed for some women who only rated their fatigue very high at baseline. All the nonexercisers (100%) experienced an increased number of days above their baseline average fatigue, whereas only 33% of the exercisers increased their number of days above baseline. The results for the worst fatigue were similar. Women who exercised had only 25% bad days compared to 86% for the nonexercisers. The trend was for exercisers to experience fewer days of high fatigue than nonexercisers, although there were no significant differences in the patterns ($\chi^2=2.0$ for worst and .222 for average fatigue, $p>.05$).

Nonexercisers showed a slight decline in the percent number of days above baseline compared to exercisers who demonstrated a much greater decline in percent number of days above baseline from the first to the third chemotherapy cycle (Table 3). Percent number of days above baseline worst fatigue, bad days, was less for exercisers:

Relationship of fatigue to other variables

No significant relationship was observed between fatigue and stage of disease, type of chemotherapy or the demographic variables. Older women showed less intensity of worst fatigue than younger women ($r = -.532$, $p = .014$), which was also observed in previous studies (Cleeland, Demetri, Glaspy, Cella, Portenoy, Crémieux, Itri, 1999; Gabrilove, Einhorn, Livingston, Winer, Cleeland, 1999).

Discussion

Consistent with previous studies, the most common pattern for fatigue was to sharply increase in the first 24-48 hours following chemotherapy (Jamar, 1989; Pickard-Holley, 1991). However, some women deviated from that pattern, and experienced prolonged periods of elevated fatigue sometimes lasting longer than 5 days. In contrast to previous findings (Irvine et al, 1994; Pickard-Holley, 1991; Richardson, 1998) fatigue in this sample was not observed to increase with the hematologic nadir. In this study the daily pattern of fatigue was measured over three cycles of chemotherapy, which differs from previous studies. Richardson and colleagues (1998) observed the pattern of fatigue over one cycle of chemotherapy and observed an increase in fatigue at the nadir in patients who were receiving bolus chemotherapy, which was not observed in this study.

Marked increases in fatigue were noted with adverse events such as infections and invasive procedures. While it seems intuitively obvious that women would experience increased fatigue following an invasive procedure, the finding that women experienced increased fatigue before the onset of neutropenic fever is intriguing. The rise in fatigue prior to the onset of illness warrants further investigation with a larger sample. Should this finding hold out in other studies, increases in fatigue may support the merits of instructing patients to maintain daily fatigue records. These records could

be used by patients to monitor their pattern of fatigue and could provide an indication of when to contact their health care provider. While this idea is not currently founded on sufficient data, it is logical that fatigue could proceed objective signs of illness.

As observed in other studies, the level of most severe fatigue decreased with each cycle of chemotherapy for exercisers (Mock et al, 1994; Schwartz et al, in press). Women who adopted exercise experienced fewer bad days of fatigue, and demonstrated decreasing fatigue over the 3 courses of chemotherapy. While this finding was observed in a few of the nonexercisers, the fatigue patterns of nonexercisers generally showed less decline in fatigue over time. The declining fatigue pattern in exercisers supports previous studies that have suggested that exercise may be an effective intervention for fatigue (Dimeo, 1997, 1997a, 1998; Mock, 1994, 1997; Schwartz, 1998)

Both exercisers and nonexercisers had wide swings in the amount of fatigue reported. This variation in fatigue reports reflects the highly variable state which is characteristic of fatigue. Initially, the exercisers appeared to experience wider swings in their fatigue than the non-exercisers. The experience of extremely high and low levels of fatigue may have helped these women reorganize their interpretation of the sensation and learn to manage their symptom. Symptom re-organization may have influenced the fatigue patterns to become smoother (less chaotic) with less amplitude (variability) observed over time and may account for the reduced fatigue observed in the exercisers.

All the women were noted to reset or re-interpret their fatigue resulting in levels of highest fatigue being lower and levels of lowest fatigue being higher. This shift away from the extreme ends of the scales suggests a response-shift (Breetvelt & Van Dam, 1991; Sprangers, 1996). The timing of when this shift in symptom appraisal occurs is unclear and may be different for each woman depending on how she interprets her fatigue symptoms. However, because the trend was for the peak in fatigue following chemotherapy to decline with each cycle of chemotherapy, it is reasonable to suspect

that many of the women were adjusting and resetting their interpretation of fatigue during the first cycle of chemotherapy. Women may be downgrading their fatigue to allow for it to get even worse and still have room on the scale to register truly bad fatigue. This downgrading of fatigue or underreporting of the symptom may explain why most of these women showed little change in their fatigue from the first measurement at baseline to posttest. The extreme swings in their fatigue may have contributed to the process of adjusting to and shifting their internal norm for fatigue.

Women who displayed the disorganized, highly variable, chaotic pattern over the 3 cycles of chemotherapy may have: a) failed to recognize and interpret their fatigue symptoms, b) failed to adjust their expectations, or c) had difficulty establishing links between self-care activities and the fatigue experienced. These women appear to not be using their fatigue to guide their symptom management efforts. Women with this pattern of fatigue may have experienced fatigue in association with other symptom clusters (e.g. pain, nausea, sleep disruption), or possibly were unable or unaware of how to manage their symptom and/or their energy.

Older women reported less fatigue, which is consistent with previous studies that report negative correlations with fatigue and other symptoms (Cleeland, et al, 1999; Gabrilove, Einhorn, Livingston, Winer, Cleeland, 1999). Younger age may explain the chaotic patterns observed in some of the plots. It is also conceivable that the younger women in this sample may not have experienced the same life stressors associated with fatigue or that they lacked the extensive life experiences of the older women to develop a schema to interpret their fatigue. Alternatively, the younger women may have experienced more life demands (family, work, social) that they were either unable or unwilling to let go.

Limitations

The generalizability of this study is limited both by the small sample and one-group design. A home-exercise program lacks the control of a supervised exercise program, but is more cost effective and generalizable to women who may be encouraged to exercise. Finally, because of the incredible variability in fatigue, the analysis was limited to a description of the patterns. A randomized clinical trial design is needed to determine differences in the pattern of fatigue.

Summary

In summary, the fatigue patterns suggest that exercise may have a positive effect on fatigue, may help women with breast cancer re-organize their interpretation of fatigue, and learn to manage their symptoms more quickly. Understanding the response-shift in fatigue may lead to future research examining how cognitive structures are formed to reorganize a patient's understanding of fatigue, and how this reorganization affects responses to measures of fatigue and other symptoms (Breetvelt & VanDam, 1991). To keep women with breast cancer functioning and participating in activities they value, it is critical that we develop interventions to reduce their fatigue.

Table 1. Pattern of peak average and worst fatigue with each chemotherapy cycle.

	N	Exercisers (n)	Non-exercisers (n)	χ^2	p
Average fatigue (n=17)					
Fatigue scores decrease with each chemotherapy cycle	11	10	1	2.88	.09
Fatigue score increase with each chemotherapy cycle	6	2	4		
Worst fatigue (n=15)					
Fatigue score decrease with each chemotherapy cycle	13	11	2	8.07	.005
Fatigue score increase with each chemotherapy cycle	2	0	2		

*Reflects only subjects who fit these patterns of fatigue.

Table 2. Range of percent number of days when worst and average fatigue scores (good days) were below baseline scores by chemotherapy cycle *.

	Cycle 1	Cycle 2	Cycle 3
Worst fatigue			
Exercisers (n=13)	4-96%	19-100%	6-100%
Non-exercisers (n=6)	4-70%	4-88%	10-25%
Average fatigue			
Exercisers (n=10)	7-76%	9-100%	10-100%
Non-exercisers (n=5)	9-65%	9-76%	7-14%

* Subjects who scored zero at baseline were not included.

Table 3. Range of percent number of days when worst and average fatigue scores were above baseline scores (bad days) by chemotherapy cycle.

	Cycle 1	Cycle 2	Cycle 3
Worst fatigue			
Exercisers (n=13)	12-95%	0-95%	0-57%
Non-exercisers (n=6)	14-90%	15-95%	24-78%
Average fatigue			
Exercisers (n=10)	4-95%	4-81%	10-88%
Non-exercisers (n=5)	26-92%	15-82%	56-92%

Figure 1. Increasing peaks in average fatigue with each cycle of chemotherapy in a woman who did not exercise and received cyclophosphamide, methotrexate and flurouracil on days 1, 21 and 43.

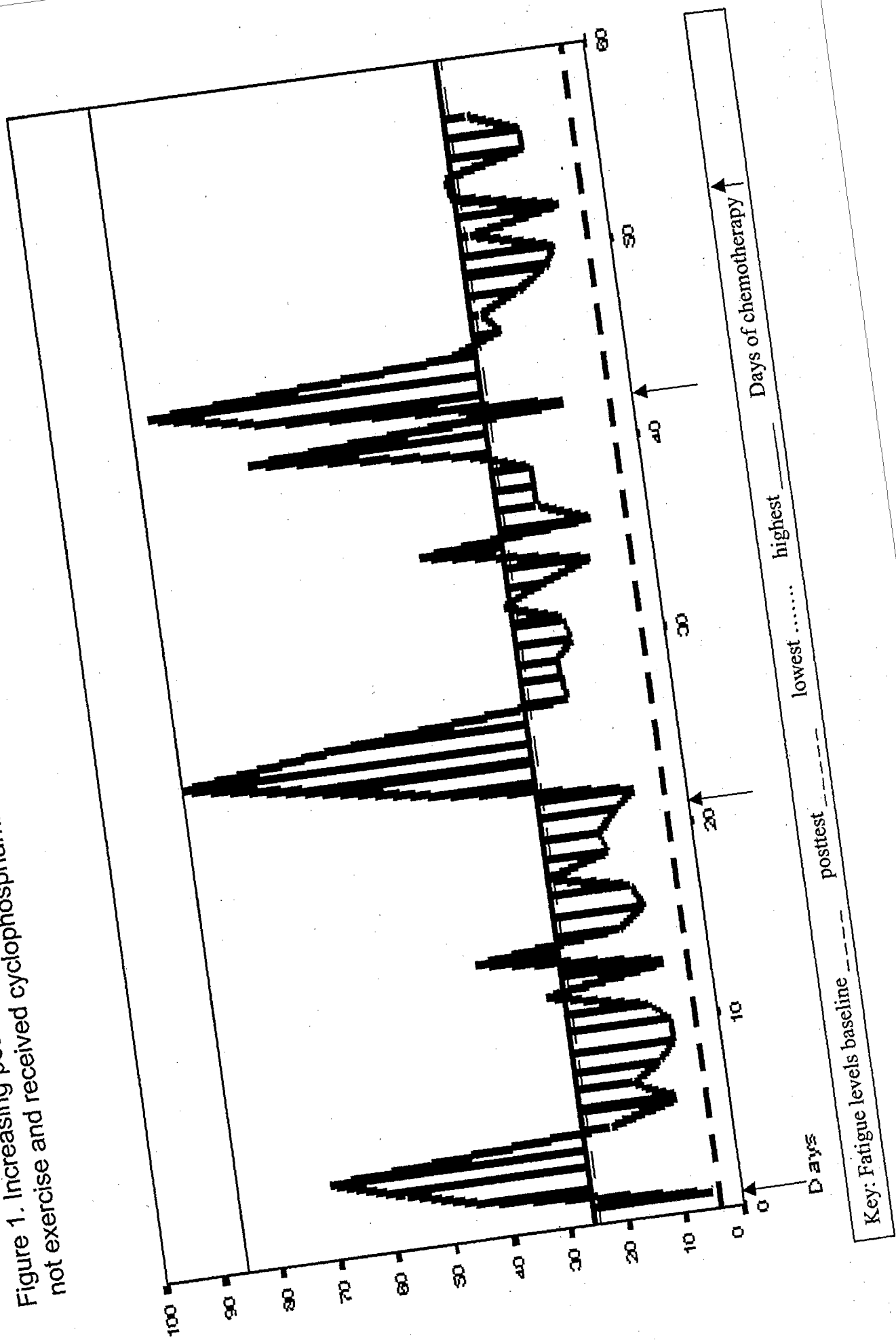
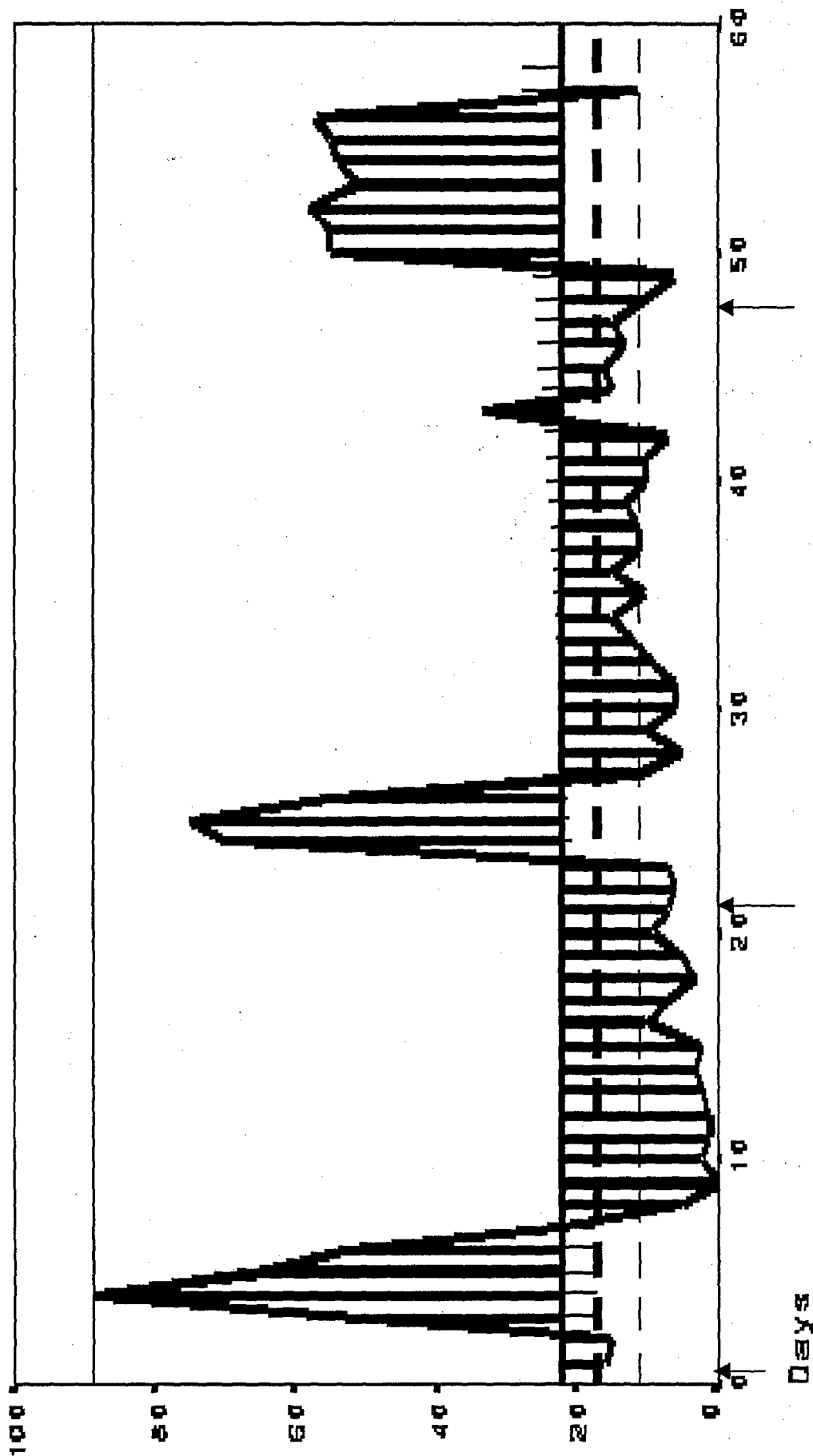


Figure 2. Delay in peak average fatigue after receiving chemotherapy observed in a woman who did not exercise and received doxorubicin and cyclophosphamide on days 1, 22 and 49.



Key: Fatigue levels baseline _____ posttest _____ lowest highest _____ Days of chemotherapy ↑

Figure 3. No increase in worst fatigue during nadir (days 16-29) and rapid increase in fatigue before and during neutropenic fever (days 50-52) in a woman who exercised and received cyclophosphamide, methotrexate and flurouracil on days 1 and 35.

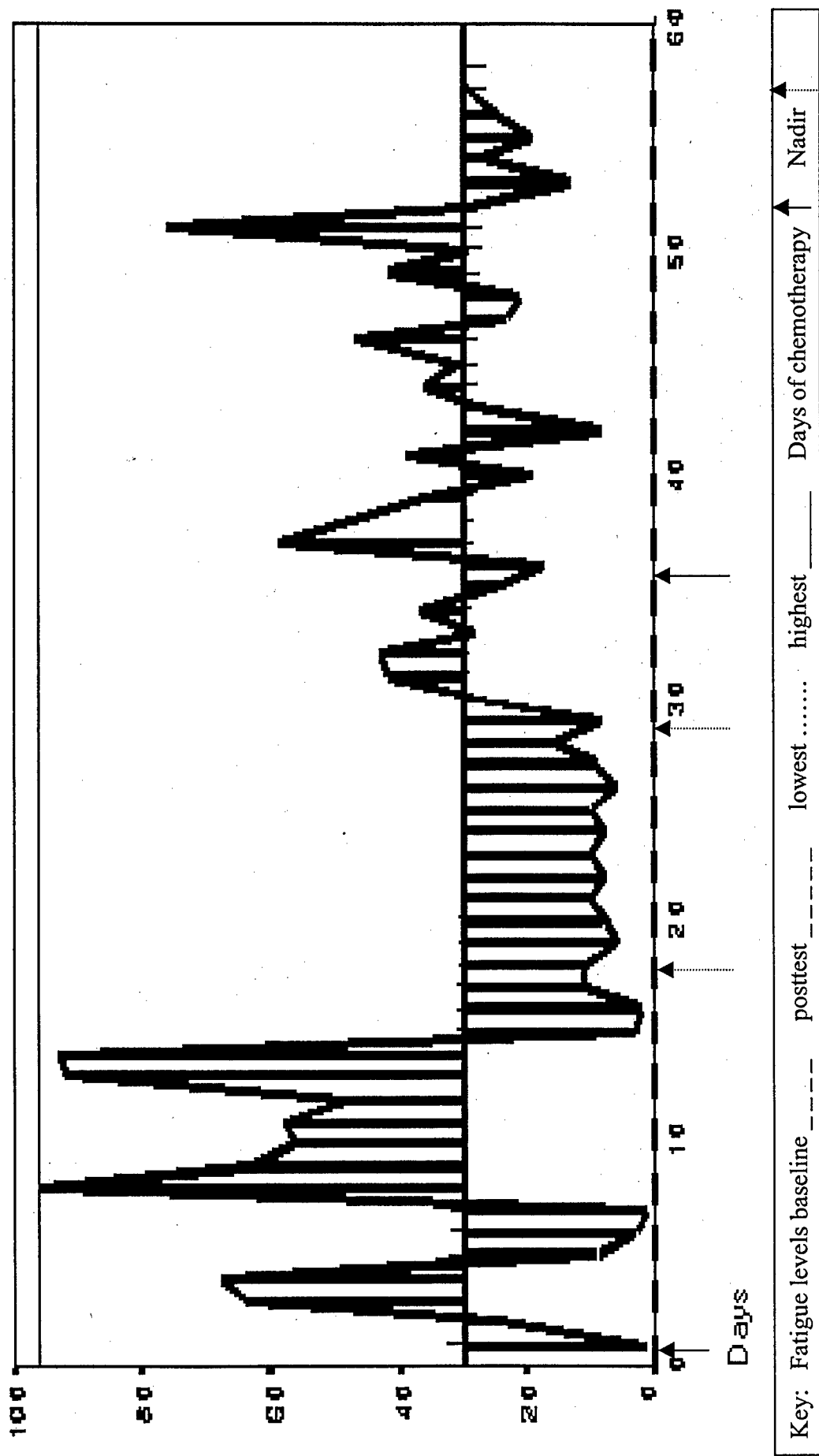
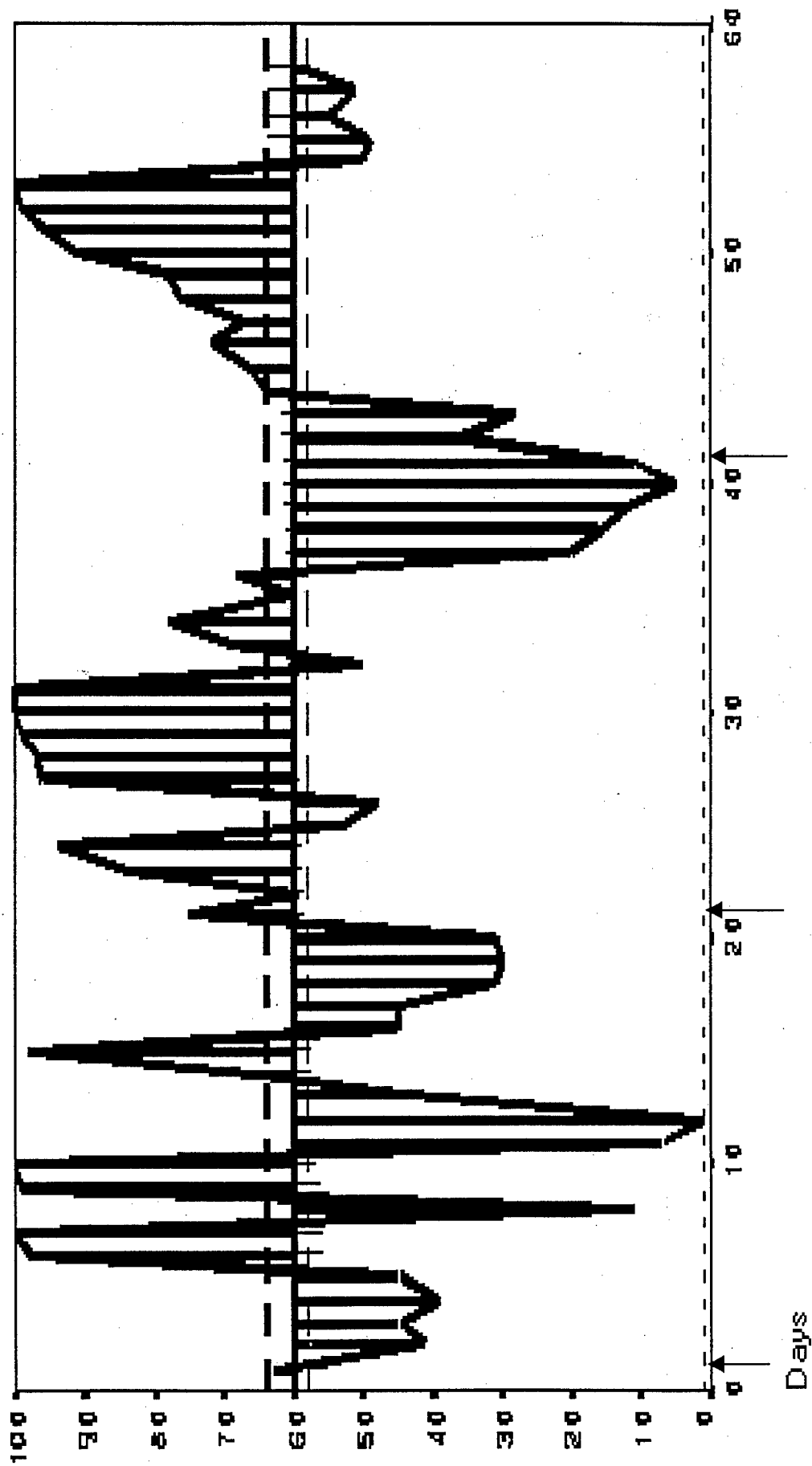


Figure 4. Chaotic pattern of worst fatigue in a woman who did not exercise and received doxorubicin and cyclophosphamide on days 1, 21 and 42. Note the delay in peak fatigue after the second dose of chemotherapy (day 42).



Key: Fatigue levels baseline ----- posttest ----- lowest highest ----- Days of chemotherapy ↑

Figure 5. Decreasing amplitude of average fatigue over time in a woman who did not exercise and received doxorubicin and cyclophosphamide on days 2, 23, and 49.

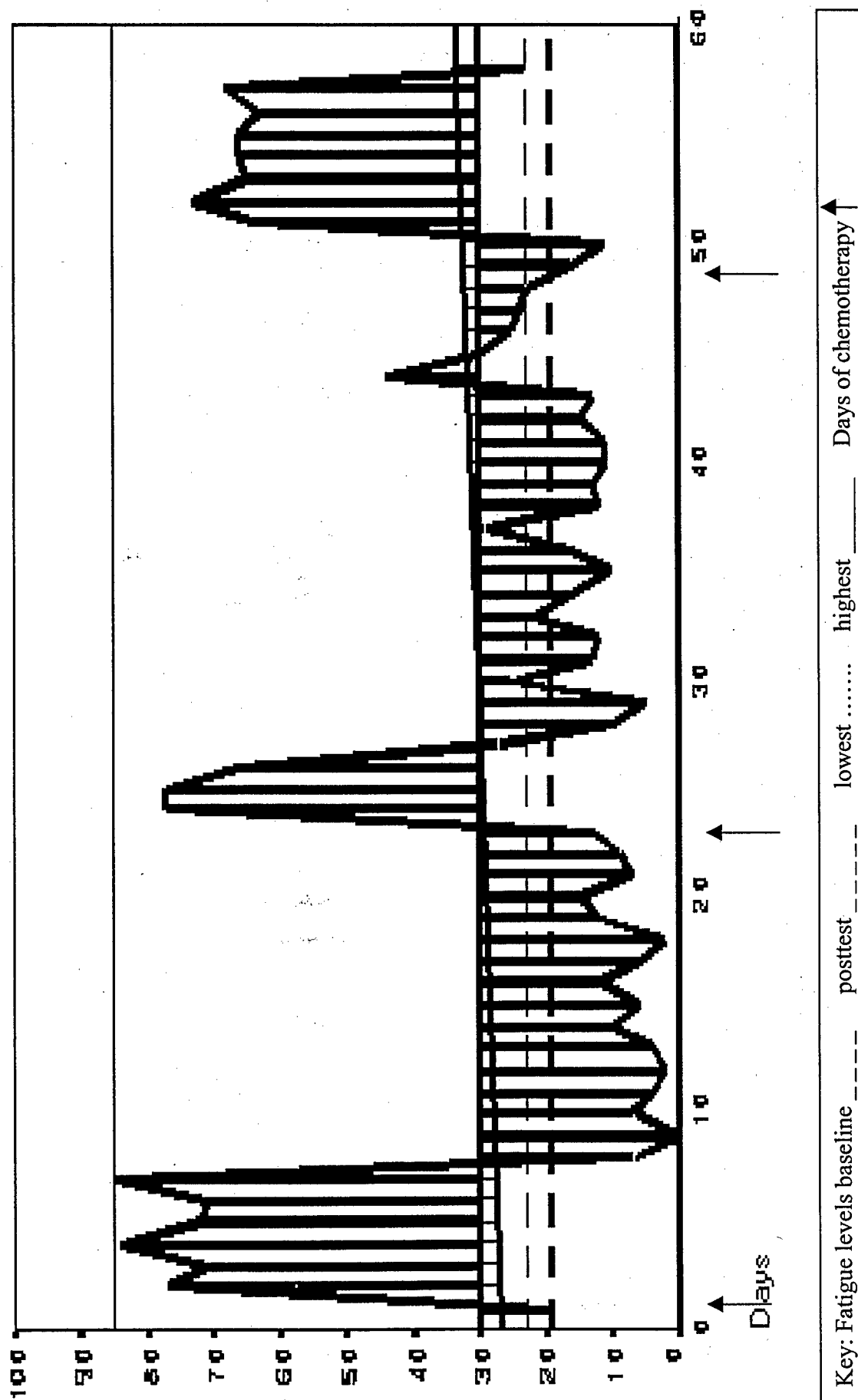
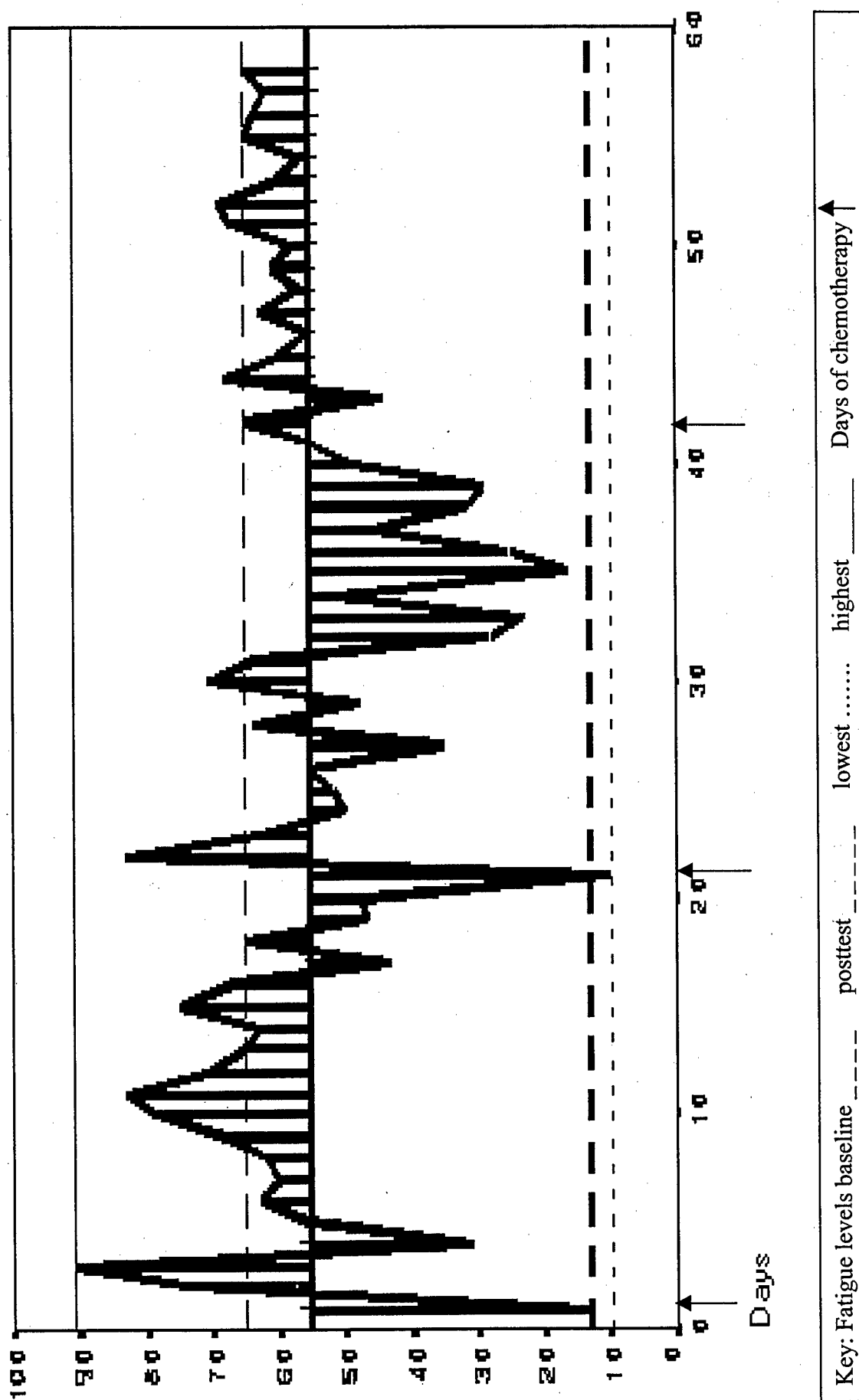


Figure 6. Decreasing number of days of highest levels of worst fatigue in a woman who exercised and received doxorubicin and cyclophosphamide on days 1, 21, and 42.



References

1. Blair, S.N., Kohl, H.W., Barlow, C.E., Paffenbarger, R.S., Gibbons, L.W., Macera, C.A. Changes in physical fitness and all-cause mortality. *JAMA*. 1995;273:1093-1098.
2. Blesch, K.S., Paice, J.A., Wickham, R., Harte, N., Schnoor, D.K., Purl, S., Rehwalt, M., Kopp, P.L., Manson, S., Coveny, S.B., McHale, M., & Cahill, M. Correlates of fatigue in people with breast or lung cancer. *Oncology Nursing Forum*. 1991;8:81-87.
3. Breetvelt, I.S., & Van Dam, F.S.A.M. Underreporting by cancer patients: the case of response shift. *Soc Sci Med*. 1991;32 (9):981-987.
4. Bruera E, MacDonald RN. Asthenia in patients with advanced cancer. *Journal of Symptom Management*. 1988;3:9-14.
5. Cella, D., Paterman, A., Passik, S., Jacobsen, P., & Breirbart, W. Progress toward guidelines for the management of fatigue. *Oncology*. 1998;12:369-377.
6. Cooper KH. A means of assessing maximal oxygen uptake. *JAMA*. 1968;203:133-38.
7. Dean, G.E., & Ferrell, B.R. Impact of fatigue on quality of life in cancer survivors. *Quality of Life-A Nursing Challenge*. 1995;4:25-28.
8. Dimeo FC, Fetscher S, Lange W, Mertelsmann R, Keul J. (1997). Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood*. 1997;90:3390-3394.
9. Dimeo FC, Tilmann MHM, Bertz H, Kanz L, Mertelsmann R, Keul J. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous stem cell transplantation. *Cancer*. 1997a;79:1717-1722.
10. Dimeo, F., Rumberger, B.G., & Keul, J. (1998). Aerobic exercise as therapy for cancer fatigue. *Medicine and Science in Sports and Exercise*. 1998;30:475-478.

11. Irvine D, Vincent L, Graydon JE, Bubela N, & Thompson L. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. *Cancer Nursing*. 1994;17:367-78.
12. Lorig, K.R., Sobel, D.S., Stewart, A.L., Brown, B.W., Bandura, A., Ritter, P., Gonzalez, V.M., Laurent, D.D., & Holman, H.R. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization. A randomized trial. *Medical Care*. 1999;37:5-14.
13. MacVicar MG, & Winningham ML. Promoting the functional capacity of cancer patients. *Cancer Bulletin* 1986;38:235-239.
14. Mock V, Burke MB, Sheehan P, Creaton EM, Winningham ML, McKenney-Tedder S, et al. A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. *Oncology Nursing Forum*. 1994;21:899-907.
15. Mock V, Dow KH, Meares CJ, Grimm PM, Dienemann JA, Haisfield-Wolfe ME, et al. An exercise intervention for management of fatigue and emotional distress during radiotherapy treatment for breast cancer. *Oncology Nursing Forum*. 1997;24: 991-1000.
16. Montoye, H.J., Kemper, H.C., Saris, W.H., & Washburn, A. (1996). *Measuring physical activity and energy expenditure*. Champaign, IL: Human Kinetics.
17. Nail, L.M., & Jones, L.S. Fatigue as a side effect of cancer treatment: Impact on quality of life. *Quality of Life-A Nursing Challenge*. 1995;4:8-13
18. Nail LM, Winningham ML. Fatigue and weakness in cancer patients: The symptom experience. *Seminars in Oncology Nursing* 1995;11:272-78.
19. Paffenbarger, R.S. Hyde, R.T., & Wing, A.L. Physical activity and incidence of cancer in diverse population: a preliminary report. *American Journal of Clinical Nutrition*. 1987;45:312-317.

20. Pambianco, G. Wing, R., & Robertson, R. Accuracy and reliability of the Caltrac accelerometer for estimating energy expenditure. *Medicine Science in Sports and Exercise*. 1990;22:858-862.
21. Pate RR, Pratt M., Blair SN, Haskell WL, Macera CA, et al. Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273:402-407.
22. Pickard-Holley S. Fatigue in cancer patients. *Cancer Nursing*. 1991;14:13-9.
23. Piper BF, Lindsey AM, Dodd MJ. Fatigue mechanisms in cancer patients: Developing nursing theory. *Oncology Nursing Forum*. 1987;14:17-23.
24. Post-White J, Schroeder L. Factors influencing breast cancer survivors' fatigue emotional state and immune function and quality of life. Proceeds from the American Cancer Society National Conference on Cancer Nursing Research, Panama City, FL, January 1997.
24. Richardson, A., & Ream, E. The experience of fatigue and to other symptoms in patients receiving chemotherapy. *European J Cancer Care*. 1996;5, Suppl. 2: 24-30
25. Schwartz, A.L. Patterns of exercise and fatigue in physically active cancer survivors. *Oncology Nursing Forum*. 1998;25:485-491.
26. Schwartz, A.L. Reliability and validity of the Schwartz Cancer Fatigue Scale. *Oncology Nursing Forum*. 1998;25:711-717.
27. Schwartz, A.L., Nail, L.M., Chen, S., Meek, P., Barsevick, A.M., King, M.E., & Jones, L.S. (in press). Fatigue patterns observed in patients receiving chemotherapy and radiotherapy. *Cancer Investigation*.
28. Sprangers, M.A. Response-shift bias: a challenge to the assessment of patients' quality of life in cancer clinical trials. *Cancer Treatment Reviews*. 1996;22 (Suppl A): 55-62.

29. Cleeland, C.S., Demetri, G.D., Glaspy, J., Cella, D.F., Portenoy, R.K., Cremieux, P.Y., Itri, L.M. Identifying hemoglobin level for optimal quality of life: Results of an incremental analysis. *Proceedings of ASCO*. 1999 ;8:574a.
30. Gabrilove, J.L., Einhorn, L.H., Livingston, R.B., Winer, E., Cleeland, C.S. Once-weekly dosing of epoetin alfa is similar to three-times weekly dosing in increasing hemoglobin and quality of life. *Proceedings of ASCO*. 1999 ;8:574a.
31. Steele B. Timed walking tests of exercise capacity in chronic cardiopulmonary illness. *Journal of Cardiopulmonary Rehabilitation*. 1996;16:25-33.
32. St. Pierre BA, Kasper CE, Lindsey AM. Fatigue mechanisms in patients with cancer: Effects of tumor necrosis factor and exercise on skeletal muscle. *Oncology Nursing Forum*. 1992;19:419-25.
33. Washburn, R.A., & LaPorte, R.E. Assessment of walking behavior: Effect of speed and monitor position on two objective physical activity monitors. *Research Quarterly for Exercise and Sports*. 1988;59:83-85.
34. Winningham ML, Nail LM, Burke MB, Brophy L, Cimprich B, Jones LS, et al. Fatigue and the cancer experience: The state of the knowledge. *Oncology Nursing Forum*. 1994;21:23-36.
35. Vogelzang, N.J., Breitbart, W., Cella, D., Curt, G.A., Groopman, J.E., Horning, S.J., Itri, L.M., Johnson, D.H., Scherr, S.L., & Portenoy, R.K., The Fatigue Coalition. Patient, Caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey *Seminars in Hematology*. 1997;34, Suppl 2: 4-12.

Abstracts

QOL: Quality of Life Management

150711

Schwartz, Anna**1999 Annual Meeting of the American Society of Clinical Oncology****Presenting Author:** Anna L. Schwartz**Institution:** University of Washington, Seattle, Washington, 98195-7266,**Address:** Box 357266, Seattle, Washington, 98195-7266**Phone:** 206-685-2267 **Fax:** 206-543-4771 **E-Mail:** annaswtz@u.washington.edu**Abstract Categories:** QOL. Quality of Life Management**Format Preference:** Slide or Poster presentation **Awards:****Audio/Visual:** Yes**Sponsor:** Julie Gralow **Sponsor Fax:** 206-616-8553**Program Director:** Robert Livingston**Effect Of Exercise On Weight Gain In Women With Breast Cancer Receiving Adjuvant Chemotherapy.**A L Schwartz¹. ¹School of Nursing, University of Washington, Seattle, Washington.

Introduction: Weight gain is commonly observed in women receiving adjuvant chemotherapy. This is not only a distressing side effect of treatment, but one that predisposes cancer survivors to other morbidities. The purpose of this study was to examine the effect of exercise on weight gain in newly diagnosed women with stage II-III breast cancer receiving either doxorubicin and cyclophosphamide (AC) or cyclophosphamide, methotrexate and fluorouracil (CMF). Procedures: Seventy-eight women were enrolled in an 8-week exercise program. Women were instructed to exercise 4 days/week between 15-30 minutes at an intensity that did not worsen their symptoms. Baseline measures were obtained before the first dose of chemotherapy. Measures included functional ability (12-minute walk), energy expenditure (Caltrac accelerometer), body weight, frequency and intensity of anorexia and nausea, and dose of exercise (frequency, intensity, and duration). Descriptive statistics were used to describe the sample and measures. T-tests were used to examine differences in weight, side effects, and functional ability. Summary: Women who exercised (N=42) maintained a constant weight from baseline to posttest (mean=150.2 lb, SD=24.5; posttest mean=150.4 lb, SD=28.5). Women who did not exercise (N=29) showed steady increases in weight (baseline mean=169 lbs SD=40.2; posttest mean=176 lbs, SD=40.2). When controlling for baseline weight, significant differences in weight gain were observed during the 3rd (p=.02) and 4th (p=.02) cycle of chemotherapy. Nonexercising women showed an increasing trend in weight over time, while the exercisers maintained relatively stable weight. The women who exercised expended an average of 77 kcal/day in exercise; exercising a mean of 33 minutes/day, 4 days/week. Neither frequency nor intensity of anorexia or nausea were associated with weight gain. Women who exercised showed significant increases in functional ability, averaging a 15% improvement compared to nonexercisers who showed an average decline in functional ability of 22.5% (p<.000). Significance: Results suggest the value of low intensity aerobic exercise for maintaining weight while receiving adjuvant chemotherapy. Promoting healthy behaviors during chemotherapy may prevent the long-term development of co-morbid conditions that reduce quality of life and cause significant morbidity and mortality in cancer survivors.

EXERCISE DOSE AND DAILY PATTERN OF FATIGUE. Anna L. Schwartz, PhD, ARNP, University of Washington, Seattle, WA 98195; Motomi Mori, PhD, and Lillian M. Nall, University of Utah, Salt Lake City, UT 84112.

Problem

Cancer treatment-related fatigue (CRF) is the most prevalent and disturbing side effect of treatment for the majority of cancer patients; often leading to declines in emotional, psychosocial and physical function. Despite this, the mechanisms underlying it are not understood, and little is known about managing CRF. Although studies with cancer patients have demonstrated positive effects of exercise on mood, side effect severity, weight gain, functional ability and quality of life, the dose of exercise on the daily pattern of CRF has not been examined.

Purpose

The purpose was to examine the daily pattern of CRF in relation to dose of exercise over the first three cycles of chemotherapy in women with breast cancer receiving either cyclophosphamide, methotrexate and fluorouracil (CMF) or Adriamycin and cyclophosphamide (AC).

Methods

Seventy-two newly diagnosed women with breast cancer were instructed in an 8-week home-based low-intensity exercise program. Measures of functional ability (12-minute walk), energy expenditure (Caltrac™ accelerometer), CRF (Schwartz Cancer Fatigue Scale, visual analogue scale) and Side Effect Severity Scale were obtained at baseline and posttest. Subjects maintained daily records of 4 types of CRF (recorded on a visual analogue scale) and type, duration and intensity of exercise.

Analysis

Descriptive statistics were used to describe the sample and measures. All daily CRF data was analyzed using unbalanced repeated measures analysis (PROC MIXED procedures, Statistical Analysis System, Version 6.12). The presence or absence of exercise, number of minutes exercised, and cumulative amount of exercise were evaluated as time-dependent covariates in the analysis.

Findings

Exercise demonstrated a strong effect on reducing fatigue intensity (Table 1). A linear relationship between fatigue and the square root of the number of minutes exercised indicated that as the number of minutes of exercise increased CRF declined. The model predicted a steeper decline in fatigue in the first hour of exercise and a linear decline between 1-2 hours of exercise. The impact of exercise on CRF appears to more immediate, although there appears to be a small carry-over effect of exercise on the next day. Baseline CRF was neither associated with number of days of exercise nor amount of exercise, suggesting that CRF level prior to beginning chemotherapy does not predict exercise. Side effect severity was associated with both exercise frequency and duration.

Implications

The impact of exercise on CRF was strong and reflects the effectiveness of low-intensity regular exercise in maintaining functional ability and reducing CRF in patients with breast cancer. The implications of these findings support the need for regular daily, low intensity exercise to reduce CRF in women with breast cancer receiving either CMF or AC.

Table 1. Least squares means & standard errors for CRF by number of minutes of exercise.

# Minutes Exercise/day	Worst fatigue	Least fatigue	Fatigue now	Average fatigue
0	50.99 (1.24)	22.85 (0.94)	47.11 (2.50)	36.89 (1.05)
1-30	47.87 (1.49)	18.69 (1.14)	42.30 (2.86)	33.55 (1.25)
31-60	43.43 (1.83)	17.29 (1.43)	36.16 (3.39)	28.47 (1.53)
>60	39.79 (3.01)	14.76 (2.44)	40.33 (5.33)	26.89 (2.56)
p value	<.0001	<.0001	.0005	<.0001

Supported in part by grants from the U.S. Army Medical Research & Materiel Command DAMD17-96-1-6171, NIH/NINRF31 NR07159, & the Oncology Nursing Foundation.

DIFFERENCES IN THE PATTERN OF CANCER-RELATED FATIGUE AND VIGOR

SPECIFIC AIMS: This paper describes the pattern of CRF and vigor in patients receiving various chemotherapy regimens and forms of radiation therapy.

BACKGROUND: Cancer-related fatigue (CRF) is a highly prevalent (affecting 40-100% of patients) and distressing side effect of cancer treatment. The intensity and prolonged duration of CRF negatively impacts quality of life. CRF is a frustrating symptom for clinicians; the mechanism is unclear and few interventions have been tested to demonstrate efficacy.

METHOD: Five studies that used the Profile of Mood States fatigue and vigor subscales were used to describe the pattern of CRF and vigor during and after treatment. These studies were selected in order to facilitate comparisons and minimize the measurement problems associated with using nonequivalent instruments.

ANALYSIS: Descriptive analyses were used to describe the samples and patterns of fatigue and vigor over time. Repeated measures analysis of variance was employed to describe differences over time. To facilitate comparisons, analytic techniques were conducted in a uniform manner across all studies. Post hoc measures were used in Study 5 to examine differences in CRF and vigor by type of chemotherapy regimen and stage of disease.

RESULTS: Each of the five studies demonstrates a pattern of CRF that is specific to chemotherapy and radiation therapy. As CRF scores peak after chemotherapy or radiation therapy, vigor scores decline; conversely, when CRF begins to decline, vigor scores rise. However, the two concepts do not mirror one another in degree of change (Table 1). Negative correlations were observed between the fatigue and vigor subscales of the POMS (range $r = -.41$ to $-.74$ in Study 1 with the smallest sample). While the pattern of fatigue and vigor differ, they are clearly related concepts; not opposite ends of a continuum.

Table 1. POMS fatigue and vigor peak and trough means and standard deviations.

	CRF		Vigor	
	Peak	Trough	Peak	Trough
Study 1 (N=25)	9.7 (8.7)	6.0 (6.9)	17.5 (7.1)	13.1 (9.6)
Study 2 (N=185)	7.8 (5.0)	6.0 (4.7)	5.5 (4.4)	6.9 (4.9)
Study 3 (N=116)	9.1 (6.1)	7.6 (5.4)	8.0 (5.4)	6.1 (5.0)
Study 4 (N=116)	9.2 (6.0)	7.2 (5.3)	8.4 (4.6)	6.2 (5.1)
Study 5 (N=61)	11.5 (7.6)	7.5 (6.9)	14.7 (6.8)	10.5 (6.5)

*Possible scores range from 0-28 (CRF) and 0-32 (vigor) for Studies 1, 5; 0-24 (CRF and vigor) Study 2; 0-20 (CRF and vigor) Studies 3, 4.

** Subjects in Studies 1 and 3 received radiation therapy. Subjects in Studies 2, 4, and 5 received chemotherapy.

Each of the studies demonstrates a pattern unique to chemotherapy and radiotherapy. CRF associated with chemotherapy peaks between 2 and 5 days after treatment and remains elevated above baseline following each cycle of chemotherapy, showing somewhat of a stair-step effect over time. Radiotherapy related fatigue shows a more gradual increase over time. CRF associated with different types of treatment (biotherapy, radiotherapy, and chemotherapy) have unique patterns that may be further influenced by person-related variable (e.g. age, gender).

CONCLUSIONS: As practitioners it is important to prepare patients for an unknown and often feared experience to allow them to prepare for and understand what to expect. Educating patients opens communications between patient and provider and reduces patient anxiety about treatment and treatment-related side effects.

EXERCISE DOSE AND DAILY PATTERN OF FATIGUE

Anna L. Schwartz, Ph.D., ARNP, University of Washington, Seattle, WA 98195, Motomi Mori, Ph.D., & Lillian M. Nail, University of Utah, Salt Lake City, UT 84112.

Problem: Cancer treatment-related fatigue (CRF) is the most prevalent and disturbing side effect of treatment for the majority of cancer patients; often leading to declines in emotional, psychosocial and physical function. Despite this, the mechanisms underlying it are not understood, and little is known about managing CRF. Although studies with cancer patients have demonstrated positive effects of exercise on mood, side effect severity, weight gain, functional ability and quality of life, the dose of exercise on the daily pattern of CRF has not been examined. **Purpose:** The purpose was to examine the daily pattern of CRF in relation to dose of exercise over the first three cycles of chemotherapy in women with breast cancer receiving either cyclophosphamide, methotrexate and fluorouracil (CMF) or Adriamycin and cyclophosphamide (AC). **Methods:** Seventy-two newly diagnosed women with breast cancer were instructed in an 8-week home-based low-intensity exercise program. Measures of functional ability (12-minute walk), energy expenditure (Caltrac™ accelerometer), CRF (Schwartz Cancer Fatigue Scale, visual analogue scale) and Side Effect Severity Scale were obtained at baseline and posttest. Subjects maintained daily records of 4 types of CRF (recorded on a visual analogue scale) and type, duration and intensity of exercise. **Analysis:** Descriptive statistics were used to describe the sample and measures. All daily CRF data was analyzed using unbalanced repeated measures analysis (PROC MIXED procedures, Statistical Analysis System, Version 6.12). The presence or absence of exercise, number of minutes exercised, and cumulative amount of exercise were evaluated as time-dependent covariates in the analysis. **Findings:** Exercise demonstrated a strong effect on reducing fatigue intensity (Table 1). A linear relationship between fatigue and the square root of the number of minutes exercised indicated that as the number of minutes of exercise increased CRF declined. The model predicted a steeper decline in fatigue in the first hour of exercise and a linear decline between 1-2 hours of exercise. The impact of exercise on CRF appears to more immediate, although there appears to be a small carry-over effect of exercise on the next day. Baseline CRF was neither associated with number of days of exercise nor amount of exercise, suggesting that CRF level prior to beginning chemotherapy does not predict exercise. Side effect severity was associated with both exercise frequency and duration. **Implications:** The impact of exercise on CRF was strong and reflects the effectiveness of low-intensity regular exercise in maintaining functional ability and reducing CRF in patients with breast cancer. The implications of these findings support the need for regular daily, low intensity exercise to reduce CRF in women with breast cancer receiving either CMF or AC.

Table 1. Least squares means & standard errors for CRF by number of minutes of exercise.

# Exercise/day	Minutes	Worst fatigue	Least fatigue	Fatigue now	Average fatigue
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p value		<.0001	<.0001	.0005	<.0001

Supported in part by grants from the U.S. Army Medical Research & Materiel Command DAMD17-96-1-6171, NIH/NINRF31 NR07159, & the Oncology Nursing Foundation.

902 ENERGY EXPENDITURE AND EXERCISE ADHERENCE IN WOMEN IN BREAST CANCER RECEIVING CHEMOTHERAPY
 Anna L. Schwartz, PhD, c-FNP, University of Utah.

Management of cancer treatment-related side effects is critical to patient's quality of life and willingness to follow treatment protocols. Exercise is recommended for many acute and chronic conditions, yet little research has examined the effects of exercise on cancer patients. The purpose of this study was to determine energy expenditure, and exercise adherence and patterns among women with breast cancer receiving chemotherapy. Subjects (N=44) were given instructions to follow an 8-week low intensity home-based aerobic exercise program. Subjects were enrolled before the first dose of chemotherapy. Caltrac™ accelerometers were used to record energy expenditure in the 12-minute walks and each exercise session. At baseline, the majority were nonexercisers (M=68%). Subjects who did not follow the exercise program (nonexercisers) showed declines in functional ability of up to 37% (M=14%, SD=12%). Those who adopted the exercise program (64% of subjects) maintained or increased their functional ability (M=9%, SD=7%). The pattern of exercise varied according to chemotherapy cycle:

	#d/wk		#min/session		Caltrac™ reading	
	M	SD	M	SD	M	SD
Chemo week	3.5	2.0	127	111	590	488
Nadir week	4.0	2.1	158*	133	689	697
Recovery week	3.7	1.6	145	129	665**	716

* p<0.01; ** p<0.05.

Exercisers reported statistically fewer and less severe side effects and symptoms than nonexercisers. A low intensity exercise program can improve patient's functional ability, side effects, and quality of life during and after chemotherapy.

Supported by DoD/DAMD 17-96-1-6171

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EFFECT OF EXERCISE ON THE PATTERN OF DAILY FATIGUE IN WOMEN WITH BREAST CANCER. Anna Schwartz, PhD, c-FNP, University of Utah, College of Nursing, Salt Lake City, UT 84112.

Problem and Purpose: Fatigue is a common and distressing symptom among cancer patients during and after treatment. Exercise plays a significant role in the prevention of disease and in the rehabilitation and control of disease progression in many chronically ill patients, and is an intervention suggested to minimize cancer related fatigue (CRF). The purpose of this study was to examine the pattern of CRF over eight weeks in women with breast cancer receiving adjuvant chemotherapy. **Theoretical Framework:** The Hypokinetic theory of disease suggests that insufficient activity contributes to the development of physical and psychological degeneration and functional changes (Kraus and Raab, 1961; Stone, 1987). This theoretical approach has formed the basis for research and treatment of chronic diseases, rehabilitation of acute diseases, and maintenance of function in aging adults over the past forty years. **Methods:** A pretest-posttest one group design was used in this study. All subjects received exercise instructions for a progressive home-based exercise program that allowed for periods of recovery and accommodated to individual cycles of chemotherapy. Daily diaries of CRF and exercise were maintained by the subjects and weekly measures of CRF were obtained (SCFS-6 and POMS fatigue and vigor subscales). **Sample:** Twenty-seven newly diagnosed women with stage I-IV breast cancer were recruited into the study before beginning chemotherapy. Subjects were young ($M = 46.6$ years) and 55% were sedentary at baseline. **Analysis:** Descriptive statistics were used to describe the sample and the results of exercise and CRF. Graphical displays of the daily plots of each subject's worst and average CRF were examined with calculations made to determine number of days above and below baseline. **Results:** Results indicated that 59.3% of the sample increased the 12-minute walk distance at posttest. Subjects who exercised ($n = 16$) demonstrated a mean percent increase in the 12-minute walking distance of 10.4% (range = 1-23.5%), while the nonexercising subjects ($n = 11$) showed an average decline of nearly 16% (range = 2-36.7%). CRF increased in the days following chemotherapy, but not during the hematologic nadir. Peaks in CRF were noted before the onset of infection. Different patterns of the worst and average CRF were observed, with less CRF observed in the exercisers. An inverted U pattern emerged in subjects who did not exercise and those who engaged in high levels of exercise. **Implications:** This low-intensity home-based exercise program was feasible for women with breast cancer receiving chemotherapy, and resulted in improved functional ability and reduced CRF in those subjects who exercised. Possibly exercise helped subjects reorganize their interpretation of CRF and learn to manage their symptom. Exercise appears to be an intervention that may improve patients' ability to manage CRF and maintain functional ability. This study supports the idea of a dose-response relationship of exercise to CRF.

EFFECT OF EXERCISE ON FATIGUE AND QUALITY OF LIFE IN WOMEN WITH BREAST CANCER

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Fatigue is a common and distressing symptom among cancer patients during and after treatment. Exercise plays a significant role in the prevention of disease and in the rehabilitation and control of disease progression in many populations of chronically ill patients. In light of improving cancer treatment and survival rates, developing interventions to maintain patients' functional ability and quality of life during cancer treatment is becoming increasingly important. Chronically ill cancer patients may enter a negative cycle of debilitation, diminished physical activity and deconditioning manifested by rapid fatigue on exertion, which has a profound effect on patients' quality of life. The purpose of this study was to examine the direct and indirect relationships of level of exercise to cancer related fatigue (CRF) and quality of life in women with breast cancer receiving chemotherapy.

A pretest-posttest one group design was used in this study. All subjects received exercise instructions for a progressive home based exercise program that allowed for periods of recovery and accommodated to individual cycles of chemotherapy. Variance in level of exercise and exercise intensity was achieved as a result of subjects adopting the program at different levels and giving subjects permission to exercise at their own pace. Twenty-seven newly diagnosed women with stage I-IV breast cancer were recruited into the study before beginning chemotherapy. Written consent was obtained and baseline measures of exercise (Caltrac accelerometer, pre- and posttest 12-minute walk), CRF (Profile of Mood States vigor-fatigue subscale [POMS-F], Schwartz Cancer Fatigue Scale [SCFS] and visual analogue scale of fatigue), quality of life (Quality of Life Index) were administered. Subjects were followed for 8-weeks with weekly phone calls. Daily diaries of CRF and exercise were maintained by the subjects. Posttest measures on all instruments were obtained. Although percent change in the 12-minute was used as a continuous variable, those subjects who increased the distance they covered in the 12-minute walk at posttest are referred to as exercisers.

The mean age of the sample was 46.6 years (range 35-57, SD = 5.92). Over one-half of the subjects (54.8%) did not exercise regularly at study entry. Results indicated that 59.3% of the sample increased the 12-minute walk distance at posttest. Subjects who exercised ($n=16$) demonstrated a mean percent increase in the 12-minute walking distance of 10.4% (range = 1-23.5%), while the nonexercising subjects ($n=11$) showed an average decline of nearly 16% (range = 2-36.7%). Total distance covered in the 12-minute walk for subjects who exercised ranged from 3324-5747 feet, and for the subjects who did not

exercise ranged from 1763-3934 feet. Mean scores at posttest on the CRF measures were 9.12 (range = 0-28) on the POMS-F and 11.32 (range = 6-26) on the SCFS. Quality of life mean scores were 56.8 (range = 28.5-76.87). To demonstrate a mediating effect of CRF, three multiple regression equations were tested using stepwise analysis. Exercise intensity and percent change in the 12-minute walk was regressed on CRF and explained 73% of the variance ($p < 0.01$). CRF was regressed on QOL and explained nearly 71% of the variance in quality of life ($p < 0.05$). When controlling for exercise, CRF still accounted for 71% of the variance in quality of life ($p = 0.05$). This regression demonstrated an inverse relationship between CRF and quality of life. Hierarchical regression analysis was performed, holding baseline quality of life constant, to determine the unique effect of percent change in the 12-minute walk. Regardless of the baseline quality of life, 23% of the variance in quality of life at post-test was directly and positively related to percent change in the 12-minute ($p < 0.01$). No differences in CRF were observed by stage of disease or type of chemotherapy.

A low intensity home based exercise program is feasible for women with breast cancer receiving chemotherapy, and resulted in improved functional ability and quality of life in those subjects who exercised. Subjects who exercised increased their functional ability and experienced less CRF and increased vigor. The greatest declines in functional ability were observed in subjects who exercised regularly at the beginning of the study and did not continue to exercise during the study period. Maintaining functional ability throughout the course of treatment may improve patients resiliency and ability to continue with activities they see as important.

Keywords: breast cancer, exercise, quality of life, fatigue, functional ability

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EFFECT OF EXERCISE ON FATIGUE AND QUALITY OF LIFE IN WOMEN WITH BREAST CANCER

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Fatigue is a common and distressing symptom among cancer patients, particularly during and after treatment. Chronically ill cancer patients may enter a cycle of debilitation, diminished physical activity and deconditioning marked by rapid fatigue on exertion. The purpose of this study was to examine the effects of low intensity exercise on fatigue and quality of life in women with breast cancer receiving chemotherapy.

Twenty-seven breast cancer patients who were beginning chemotherapy were instructed in a self-administered, low intensity, home exercise program for eight weeks. Subjects ranged in age from 35 to 57, with the majority of subjects not exercising before beginning the study. 60% of the sample exercised, as evidenced by increasing the distance walked in 12-minutes at the end of the study. Subjects exercised 3-6 days a week for 15 minutes to over an hour.

Results indicated that exercise decreased fatigue and improved quality of life in those persons who exercised regularly throughout the study period. No difference in exercise or CRF was observed by type of chemotherapy subjects were receiving, stage of breast cancer, age or prior exercise history. This study suggests that exercise improves breast cancer patients quality of life by decreasing their fatigue, which may help patients to continue with activities they feel are important.



DEPARTMENT OF THE ARMY
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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y)

1 Apr 03

MEMORANDUM FOR Administrator, Defense Technical Information
Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir,
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FOR THE COMMANDER:

Encl


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